Single Technology Appraisal

Dupilumab for treating moderate to severe chronic obstructive pulmonary disease [ID6235]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Sanofi:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Asthma & Lung UK
   b. Grainne d'Ancona, Consultant Pharmacist – clinical expert, nominated by British Thoracic Society
   c. Richard Russell, Head of Dept Peter Gorer Dept of Immunobiology and Clinical Reader in Respiratory Medicine, Chair of British Thoracic Society – clinical expert, nominated by Sanofi
   d. Richard McCabe – patient expert, nominated by Asthma & Lung UK

4. **External Assessment Report** prepared by BMJ Group

5. **External Assessment Report – factual accuracy check**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Dupilumab for treating moderate to severe chronic obstructive pulmonary disease [ID6235]

Document B
Company evidence submission

October 2024

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B.1. Decision problem, description of the technology and clinical care pathway

Disease overview and burden

- COPD is among the top five leading causes of death in England and mortality rates for respiratory diseases in the UK are amongst the highest in Europe.
- Prevalence of COPD in people aged ≥40 years in England is estimated at 4.9%. The number of patients with diagnosed COPD in 2022/23 was 1,151,474.
    - Of these, 13,826 patients are estimated to have Type 2 inflammation and experiencing exacerbations whilst on triple therapy.
- COPD is a complex and heterogeneous respiratory disease characterised by a combination of injury to and remodelling of the airways, lung parenchyma and lung vasculature.
    - The subgroup of patients with Type 2 inflammation (as measured by blood eosinophil [EOS] counts ≥300 cells/μL) are associated with more severe disease, e.g., more frequent exacerbations and hospital readmissions.
- Patients with COPD experience progressive airflow limitation, leading to increased dyspnoea (breathlessness), disability and premature death.
- Exacerbations - episodic flare-ups of respiratory symptoms - are considered sentinel events that drive further disease progression, and:
    - individually carry a significant risk of mortality,
    - cause further irreversible lung damage and airflow limitation,
    - are associated with an increased risk of subsequent exacerbations, cardiovascular (CV) events, and a higher symptom burden.
- COPD detrimentally affects patients' daily activities and mental health, leading to decreased productivity.
- The treatment of COPD carries substantial healthcare resource use (HCRU) in the UK, incurring an estimated annual £3.9 billion total direct costs in 2023, including:
    - £1.4 billion exacerbation costs
    - £0.7 billion treatment costs

Clinical pathway of care

- Patient care for COPD spans the range of community, primary, secondary and acute settings.
- Established guidelines for the treatment of COPD include smoking cessation, vaccination, pulmonary rehabilitation and inhaler therapies.

Unmet need

- Type 2 inflammation in COPD is associated with a higher risk of exacerbations and lung function decline.
- A large proportion of COPD patients continue to exacerbate and experience debilitating symptoms and poor quality of life despite maximal inhaled triple therapy. Such patients have limited further treatment options, and are at high risk of progression and death.

- There is an unmet need for a targeted, effective and well-tolerated treatment that can provide significant clinical improvements in exacerbations, lung function, HRQoL and symptoms in patients with uncontrolled COPD despite triple therapy, particularly those with Type 2 inflammation who experience a higher burden and worse prognosis.

Proposed population for dupilumab treatment

It is anticipated that dupilumab would be used according to its licensed indication; as add-on maintenance treatment for uncontrolled COPD characterised by raised blood EOS, on an inhaler combination of ICS, LABA and LAMA.

The definition of the population is therefore COPD with:

- ≥2 moderate or ≥1 severe historical exacerbations within 12 months (uncontrolled)
- ≥300 cells/μL blood EOS count (Type 2 inflammation)
- Treatment with a combination of ICS, LABA and LAMA (triple therapy), or LABA and LAMA (if ICS not appropriate)

B.1.1. Decision problem

This single technology appraisal evaluates the clinical- and cost-effectiveness of dupilumab as a treatment option for chronic obstructive pulmonary disease (COPD). In the UK, dupilumab (Dupixent®) is indicated "in adults as add-on maintenance treatment for uncontrolled COPD characterised by raised blood eosinophils (EOS) on a combination of an inhaled corticosteroid (ICS), a long-acting beta2- agonist (LABA), and a long-acting muscarinic antagonist (LAMA)[i], or on a combination of a LABA and a LAMA[ii] if ICS is not appropriate".(1, 2)

The final scope for dupilumab in COPD was issued by the National Institute for Health and Care Excellence (NICE) in August 2024.The key evidence in this submission is based on the results of BOREAS and NOTUS, two replicate phase III randomised controlled trials (RCTs) that evaluated the efficacy and safety of dupilumab + background therapy versus background therapy alone in adults with COPD and Type 2 inflammation (blood EOS ≥300 cells/μL) who were uncontrolled (≥2 moderate or ≥1 severe historical exacerbations within 12 months) on triple therapy or double therapy if ICS is not appropriate (Section B.2). The decision problem addressed in this submission is summarised in Table 1.

[i] The combination of an ICS, a LABA and a LAMA is typically referred to as 'triple therapy'
[ii] The combination of a LABA and a LAMA is typically referred to as 'double therapy'

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with moderate to severe COPD and raised EOS who have uncontrolled disease on triple inhaled therapy or double therapy where ICS is not appropriate	Adults with uncontrolled COPD (≥2 moderate or ≥1 severe historical exacerbations within 12 months) with raised blood eosinophils (EOS ≥300 cells/µL), on triple therapy (LABA + LAMA + ICS) or double therapy (LABA + LAMA) if ICS is not appropriate.	The scope wording anticipated the label, which became available after the final scope was issued and does not include the term 'moderate to severe' or provide definitions for 'uncontrolled' or 'raised EOS'. We have clarified these terms with a definition of 'uncontrolled' aligned to the pivotal trial inclusion criteria for prior exacerbations. (≥2 moderate or ≥1 severe historical exacerbations within 12 months). This is also in line with GOLD group E criteria. In addition, 'raised EOS' from the scope is defined as ≥300 blood eosinophils/µL. Therefore, the population is in line with the intention of the final scope to reflect the full licence.(1, 2)
Intervention	Dupilumab as an add-on to triple inhaled therapy or double therapy where ICS is not appropriate	Per NICE scope	NA
Comparator(s)	• Standard care without dupilumab (triple inhaled therapy or double therapy where ICS is not appropriate) • Roflumilast in combination with a long-acting muscarinic antagonist, a long-acting beta-2 agonist and an inhaled corticosteroid (for people who had 2 or more exacerbations in the previous 12 months despite triple inhaled therapy) • Azithromycin	• Standard care without dupilumab (triple inhaled therapy or double therapy where ICS is not appropriate) • Roflumilast in combination with a long-acting muscarinic antagonist, a long-acting beta-2 agonist and an inhaled corticosteroid (for people who had 2 or more exacerbations in the previous 12 months despite triple inhaled therapy) Azithromycin is not considered as a comparator in the submission.	As detailed in Section B.1.3.2.3 and B.3.2.4.3, azithromycin is not considered as a comparator in the submission because it: • Lacks clinical evidence supporting use in the dupilumab-eligible population.(3-5) • Is not approved for the treatment of COPD in England.(6) Off-label use is recommended by NICE; however, use is limited to non-smokers who continue to have ≥4 exacerbations per year, which differs from the dupilumab-eligible population.(7) • Has a high risk of severe AEs, including CV events, imposes additional testing and ongoing monitoring and has a high potential for the development of antibiotic resistance, limiting its use in clinical practice.(3, 4, 7-12)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			• Is being reviewed by the EMA with the aim of restricting its use due to concerns over antibiotic resistance, which is also a key concern of the UK government and NHS England.(13, 14)
Outcomes	The outcome measures to be considered include: • Lung function • Incidence and severity of acute exacerbations • Symptom control • Mortality • AEs of treatment • HRQoL	Per NICE scope	NA
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account	Per NICE scope	NA
Subgroups to be considered	If the evidence allows, the following subgroups of people will be considered: • High EOS (≥500 cells/μL) • High FeNO (≥20 ppb)	Per NICE scope	NA
Special considerations including issues related to equity or equality	NA	NA	NA

AE = adverse event; COPD = chronic obstructive pulmonary disease; EOS = eosinophils; FeNO = fractional exhaled nitric oxide; HRQoL = health-related quality of life; ICS = inhaled corticosteroids; NA = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; ppb = parts per billion; PSS = Personal Social Services; QALY = quality-adjusted life year

B.1.2. Description of the technology being evaluated

A description of dupilumab, the technology being appraised, is presented in Table 2. The summary of product characteristics and UK public assessment report for dupilumab in COPD can be found in Appendix C.

Table 2. Technology being evaluated

UK approved name and brand name	Dupilumab (Dupixent®)
Mechanism of action	Dupilumab is a recombinant human IgG4 monoclonal antibody that inhibits IL-4 and IL-13 signalling.(1, 2) Dupilumab inhibits IL-4 signalling via the Type I receptor, and both IL-4 and IL-13 signalling through the Type II receptor.(1, 2) IL-4 and IL-13 are major drivers of human Type 2 inflammatory disease, such as AD, asthma, CRSwNP, PN, EoE and COPD.(1, 2) Blocking the IL-4/IL-13 pathway with dupilumab in patients decreases many of the mediators of Type 2 inflammation.(1, 2)
Marketing authorisation/CE mark status	EMA marketing authorisation approval for dupilumab in adults with COPD was received on 28 June 2024. UK marketing approval was granted by the MHRA on 9 September 2024 following a submission through the European Commission Decision Reliance Procedure.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Dupilumab is indicated in adults as add-on maintenance treatment for uncontrolled COPD characterised by raised blood EOS 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.(1, 2)
Method of administration and dosage	The recommended dose of dupilumab for adult patients is 300 mg given every other week.(1, 2) Dupilumab is self-administered by SC injection into the thigh or abdomen, except for 5 cm around the navel, using a single-use pre-filled syringe or pen.(1, 2) If the injection is being administered by somebody else, the upper arm can also be used.(1, 2)
Additional tests or investigations	No additional tests or monitoring beyond those already recommended for patients with COPD are required.
List price and average cost of a course of treatment	£1,264.89 per pack of two pre-filled pens or pre-filled syringes £16,500 PPPY
Patient access scheme (if applicable)	The current PAS is a simple discount of [redacted]% representing £[redacted] per pack or £[redacted] PPPY. In addition to the simple discount patient access scheme, dupilumab is eligible for VPAG payments. This represents an additional 15.3% (DHSC's estimate as of December 2023) rebate on net sales of the product in 2025.

AD = atopic dermatitis; COPD = chronic obstructive pulmonary disease; CRSwNP = chronic rhinosinusitis with nasal polyps; DHSC = Department of Health and Social Care; EMA = European Medicines Agency; EoE = eosinophilic esophagitis; EOS = eosinophils; ICS = inhaled corticosteroids; IgG = immunoglobulin G; IL = interleukin; LABA = long-acting beta2-agonist; LAMA = long-acting muscarinic antagonist; MHRA = Medicines and Healthcare products Regulatory Agency; PAS = patient access scheme; PN = prurigo nodularis; PPPY= per patient per year; SC = subcutaneous; UK = United Kingdom; VPAG = voluntary scheme for branded medicines pricing, access and growth

B.1.3. Health condition and position of the technology in the treatment pathway

B.1.3.1. Disease overview

B.1.3.1.1. Introduction to COPD

COPD is among the top five leading causes of death in England,(15, 16) and mortality rates for respiratory diseases in the UK are amongst the highest in Europe.(17) The prevalence of COPD has been rising in the UK and is projected to further increase in the coming decades due to continuing exposure to risk factors and an ageing population (Section B.1.3.1.2).(3, 18, 19) COPD thus represents an important public health challenge in England, which is reflected in numerous UK government and NHS England policy documents.(20-23)

COPD is a complex and heterogeneous respiratory disease characterised by a combination of injury to and remodelling of the airways, lung parenchyma and lung vasculature.(3, 24) This results in progressive airflow limitation, leading to increased dyspnoea (breathlessness), disability and premature death (Section B.1.3.1.3).(24) Common symptoms of COPD include dyspnoea, chronic cough, sputum production, wheezing, chest tightness, exercise intolerance and episodic flare-ups of respiratory symptoms, known as exacerbations.(3) COPD exacerbations are considered sentinel events that drive further disease progression, individually carry a significant risk of mortality, cause further irreversible lung damage and airflow limitation, and are associated with an increased risk of subsequent exacerbations, cardiovascular (CV) events, as well as higher symptom burden.(25-30)

Importantly, COPD is a progressive disease characterised by chronic inflammation and exacerbations that progressively (and irreversibly) damage the lungs (Section B.1.3.1.3).(3, 31) The resulting reduced lung function is associated with more severe symptoms and further exacerbations, leading to progressively greater (and more rapid) lung function decline.(3, 27, 31) Progressive disease is also characterised by the development of comorbid conditions, including cardiovascular, metabolic, musculoskeletal and psychological diseases (Section B.1.3.1.3), making the management of patients more complex and adding to the morbidity and mortality associated with COPD.(32) COPD patients have a high mortality rate.(30) The main drivers for mortality are exacerbations, respiratory failure and comorbid cardiovascular disease.(30)

A significant proportion of patients with COPD have Type 2 inflammation (defined as blood EOS ≥300 cells/µL), which is associated with an increased risk of exacerbations and a higher rate of lung function decline over time compared to those without Type 2 inflammation.(30) Patients with COPD characterised by Type 2 inflammation (blood EOS ≥300 cells/µL) are the target population for this submission.

COPD has substantial detrimental effects on the health-related quality of life (HRQoL) of both patients and their caregivers, driven by persistent symptoms and exacerbations (Section B.1.3.1.4).(28, 33-35) COPD is also associated with considerable healthcare resource use (HCRU) and other direct costs to the NHS, as well as high indirect costs due to absenteeism, reduced productivity and early retirement among both patients and caregivers (Section B.1.3.1.5).(35-39)

Beyond the combination of an ICS, LABA and LAMA as an approach to medical management of COPD, referred to as triple inhaled therapy, there have been few significant innovations in the pharmacological treatment of COPD over the last 10 years (Section B.1.3.2). Despite treatment with triple inhaled therapy, almost two-thirds of patients with COPD continue to experience moderate to severe exacerbations.(26, 40) As a result, there is an unmet need for a targeted, effective and well-tolerated treatment that can provide significant clinical improvements in exacerbations, lung function, HRQoL and symptoms in patients with uncontrolled COPD on triple therapy. This is particularly the case for patients with Type 2 inflammation who experience a higher burden and worse prognosis.(41, 42) There are currently no therapies recommended in England for patients with COPD with Type 2 inflammation who continue to exacerbate despite triple therapy.

Diagnosis and assessment

Despite the fact that COPD is a serious, common and preventable disease, there is extensive underdiagnosis and misdiagnosis which can lead to patients receiving no or incorrect treatment.(3) This was highlighted in the second annual survey of people with COPD in the UK conducted by Asthma and Lung UK in 2022.(39) Time to diagnosis was long for many patients, with 12.4% of respondents (1 in 8) waiting 10 or more years for a diagnosis.(39)

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2024 Global Strategy for the Diagnosis, Management and Prevention of COPD and the NICE 2019 guidelines for the diagnosis and management of COPD in people ≥16 years of age, a diagnosis of COPD may be considered based on the presence of risk factors or symptoms, including progressive, persistent dyspnoea that is worse with exercise, recurrent wheeze, chronic cough that may be intermittent or that may be productive, and recurrent lower respiratory tract infections (bronchitis).(3, 7) To confirm a COPD diagnosis, spirometry showing the presence of persistent airflow obstruction is required.(3, 7) Both NICE and GOLD recommend post-bronchodilator testing, with a ratio of forced expiratory volume in the first second (FEV_1) to forced vital capacity (FVC) <0.7 indicative of airflow obstruction.(3, 7) The severity of airflow obstruction is classified into four grades, based on post-bronchodilator FEV_1, with grade 4 being the most severe (Table 3).(3, 7)

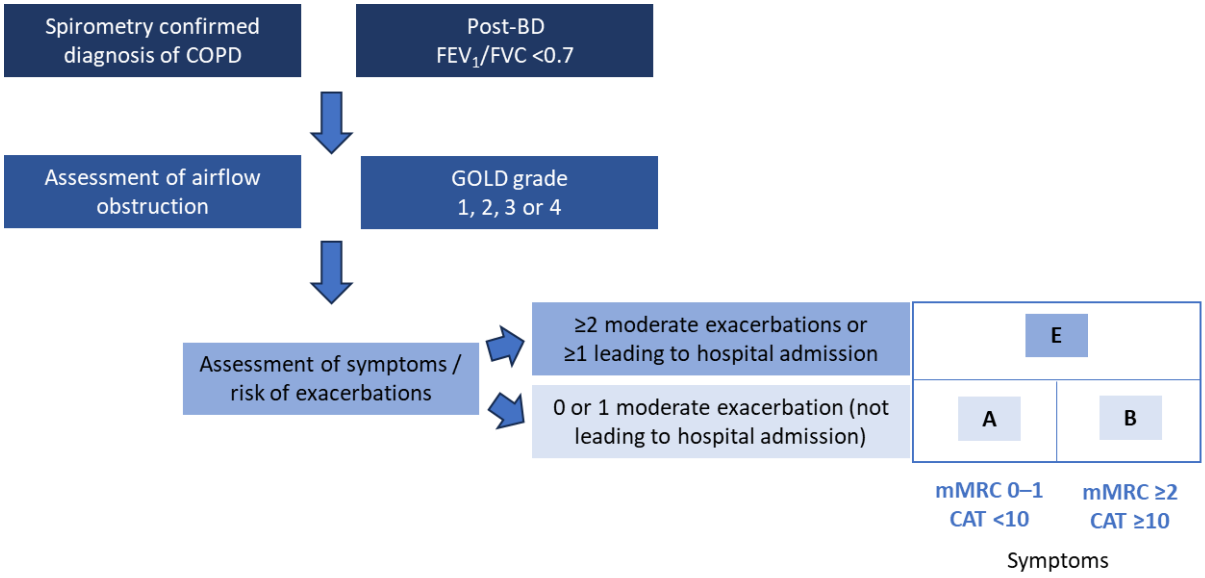
Table 3. Gradation of severity of airflow obstruction in COPD by GOLD and NICE

Grade	Post-bronchodilator FEV_1 (% reference)
1 (mild)	FEV_1 ≥80% of predicted
2 (moderate)	FEV_1 50% to 79% of predicted
3 (severe)	FEV_1 30 to 49% of predicted
4 (very severe)	FEV_1 <30% of predicted

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in the first second
Source: GOLD 2024(3); NICE 2019(7)

Airflow obstruction alone is a poor predictor of a patient's future risk of exacerbations and appropriate initial treatments.(3) For this reason, GOLD developed the ABE assessment tool, which recognises the importance of exacerbations alongside symptom burden and airflow obstruction, and classifies patients into one of three lettered groups (A, B or E; Figure 1), in order to recommend appropriate initial treatments.(3) Patients in GOLD group E (with an exacerbation history of ≥2 moderated exacerbations or ≥1 severe exacerbation, in one year) may be considered to have a worse prognosis, and broadly represent the target population for this submission.(3)

Figure 1. The GOLD ABE assessment tool



BD = bronchodilator; CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in the first second; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; mMRC = modified Medical Research Council
Source: GOLD 2024(3)

The severity of exacerbations is classified most simply by GOLD and NICE based on the level of treatment required, as defined in Table 4.(3, 7) Patients in GOLD group E have a history of ≥2 moderate exacerbations or ≥1 severe exacerbation and classification is independent of symptom burden.(3)

Table 4. Classification of COPD exacerbations by severity

Severity	Definition based on the level of treatment required
Mild	An exacerbation treated with short-acting bronchodilators only
Moderate	An exacerbation treated with short-acting bronchodilators and OCS ± antibiotics
Severe	An exacerbation that requires hospitalisation or visits to the ED; may be associated with acute respiratory failure

COPD = chronic obstructive disorder; ED = emergency department; GOLD = Global Initiative for Chronic Obstructive Lung Disease; OCS = oral corticosteroid
Source: GOLD 2024(3); NICE 2019(7)

For the assessment of symptom burden beyond the "ABE" classification, GOLD recommends the use of multidimensional questionnaires such as the COPD Assessment Test (CAT), COPD Control Questionnaire (CCQ), modified Medical Research Council (mMRC) dyspnoea scale and St. George's Respiratory Questionnaire (SGRQ).(3)

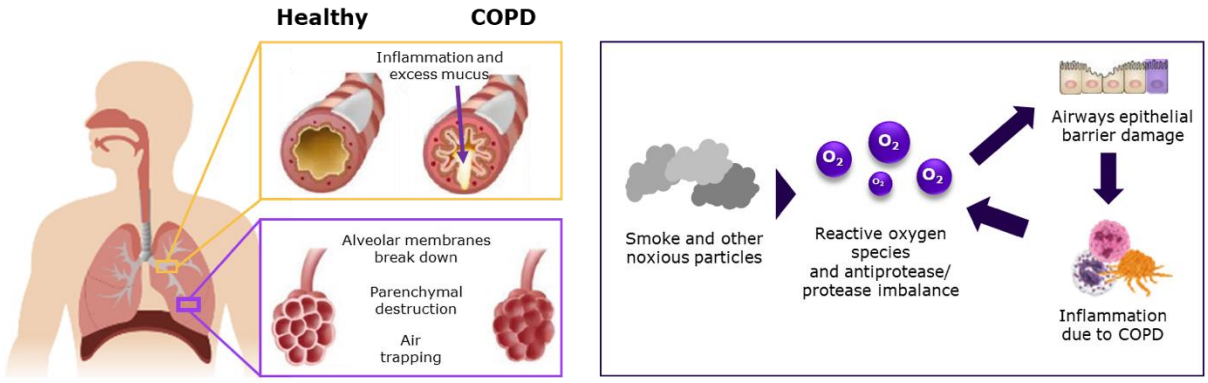
Prognostic indicators for COPD are summarised in the recently updated NICE Clinical Knowledge Summary for COPD, highlighting severity of airflow obstruction, smoking status, severity of symptoms, chronic hypoxia and/or cor pulmonale, low BMI, frequency and severity of exacerbations, hospital admission, multimorbidity and frailty.(43)

Pathology

The primary risk factor associated with the development of COPD is the inhalation of toxic particles and gases, such as tobacco smoke, biomass fuel, air pollution or occupational dust.(3) Lung damage invokes inflammatory processes, that may become pathological over time.(3) Host factors can also increase the risk of COPD, including impaired lung growth/development during gestation, childhood or adolescence and accelerated lung function decline in later life.(3)

Ongoing and progressive COPD is maintained and aggravated by chronic inflammation, which leads to airway remodelling, goblet cell hyperplasia, mucus overproduction and parenchymal destruction (emphysema; Figure 2).(3, 24, 44)

Figure 2. Pathology of COPD



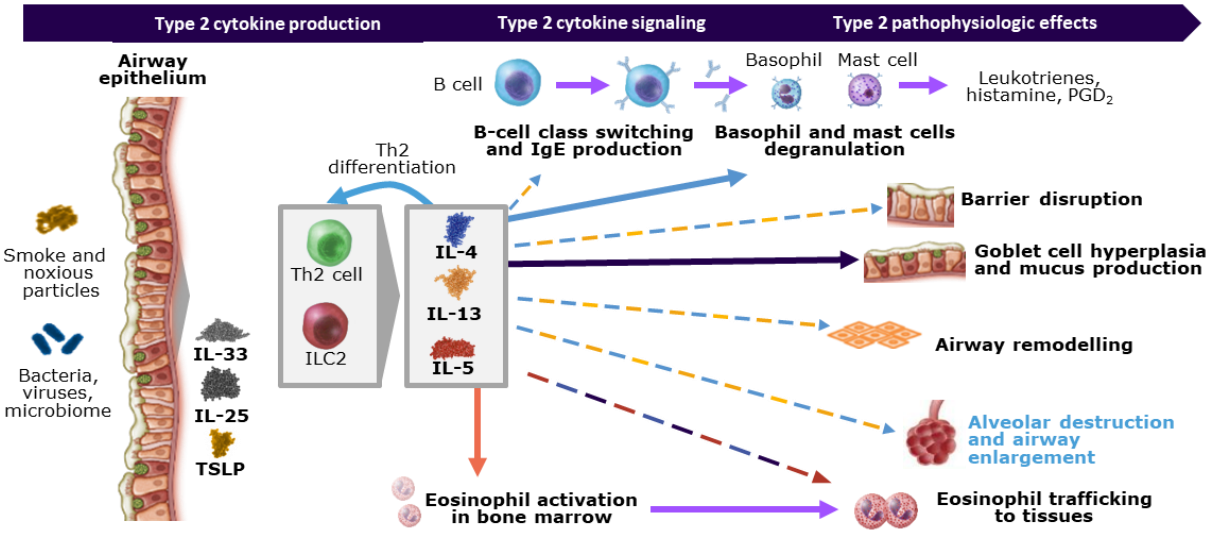
COPD = chronic obstructive pulmonary disease
Source: Adapted from Barnes 2019(44)

Inflammation in COPD variably presents with increased levels of eosinophils, neutrophils, macrophages, lymphocytes in the airways, lung parenchyma and pulmonary vasculature.(3, 44) Such inflammation may be chronic, but also may increase in association with exacerbations. COPD may be associated with by Type 1 or Type 2 inflammation, and features of each may mediate COPD pathologies:

- Type 1 (or neutrophil-associated) inflammation in COPD is characterised by an inflammatory response primarily involving neutrophils.(45) COPD with Type 1 inflammation is not the target population for this submission.
- Type 2 (or eosinophilic) inflammation occurs in up to 40% of COPD patients.(46-50) Epithelial cells lining the airways release the cytokine interleukin (IL)-33, which attracts T-helper Type 2 (Th2) and innate lymphoid Type 2 (ILC2) immune cells.(44, 51, 52) These cell types secrete Type 2 cytokines (e.g., IL-4, IL-5, IL-13), leading to eosinophil production in the bone marrow and recruitment to the lung, and activation of multiple other immune cell types including alternatively activated macrophages.(44, 51, 52) IL-4 and IL-13 are involved in key pathological processes in COPD, including airway remodelling, epithelial barrier dysfunction, goblet cell hyperplasia, mucociliary dysfunction and mucus hypersecretion (Figure 3).(53)

As described in Section B.1.2, dupilumab is a recombinant human IgG4 monoclonal antibody that inhibits IL-4 and IL-13 signalling and therefore targets Type 2 inflammation in COPD.

Figure 3. Overview of Type 2 inflammation in COPD



COPD = chronic obstructive pulmonary disease; Ig = immunoglobulin; IL = interleukin; ILC2 = group 2 innate lymphoid cell; PGD2 = prostaglandin D2; Th2 = helper 2 T cell; TSLP = thymic stromal lymphopoietin
Source: Adapted from Fieldes 2021(53) and Gandhi 2016(54)

Biomarkers of Type 2 inflammation

Blood eosinophil counts

GOLD has recognised blood EOS counts (at ≥100 and ≥300 cells/μL thresholds) as a biomarker of Type 2 inflammation that can aid the identification of patients at a higher risk of exacerbations as well as predict response to ICS therapy (add-on; triple therapy).(3) Patients with COPD and raised blood EOS experience accelerated lung function decline (Section B.1.3.1.3), an increased risk of exacerbations (Section B.1.3.1.3) and higher healthcare utilisation and costs (Section B.1.3.1.5).

Fractional exhaled nitric oxide (FeNO)

Emerging evidence also supports the use of FeNO levels as a biomarker for Type 2 inflammation, where it may be indicative of IL-13 activity specifically.(42, 55) Raised FeNO, particularly in association with a raised blood EOS count, may help predict patients at higher risk of severe exacerbations, although evidence on this associated is still evolving.(42, 55)

B.1.3.1.2. Epidemiology of COPD

Estimates of the prevalence of COPD vary across the world, primarily due to the different definitions used to describe the disease, but in England the likely conservative prevalence is 4.9% (as described below).(19) The NICE 2019 guidelines and GOLD 2024 global strategy state that COPD should be diagnosed in people with clinical symptoms confirmed by airflow obstruction, defined as an FEV_1/FVC ratio <0.7.(3, 7) However, there is no fixed threshold for airflow obstruction and alternative definitions lead to variance in the estimated prevalence of COPD, including in the UK.

A study published in 2023 using linked data from the Clinical Practice Research Datalink (CPRD) Aurum and Hospital Episode Statistics (HES) Admitted Patient Care (APC) databases (N=12,745,793) calculated the prevalence of COPD in adults aged ≥40 years between 2000 and 2019.(19) Over the 20-year observation period, COPD point prevalence increased.(19) The authors concluded that the best estimate of the prevalence of diagnosed COPD in people aged ≥40 years in England in 2019 was 4.9%.(19) Based on the estimated size of the population in England in 2019 published by the Office for National Statistics (ONS), this equates to approximately 1.4 million people with diagnosed COPD in England (rising to 1.9 million when undiagnosed people are also included).(19) It should be noted that this estimate is higher than the QOF prevalence (all ages) published by the Office for Health and Improvement Disparities ('Fingertips') for 2018/2019 (1,144,151 people) and 2022/2023 (1,151,474 people).(56)

Dupilumab is indicated in adults as add-on maintenance treatment for uncontrolled COPD (≥2 moderate or ≥1 severe historical exacerbations within 12 months) characterised by raised blood EOS (≥300 cells/μL) 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.(1, 2) To calculate the potential accessible number of COPD patients anticipated to be eligible for treatment with dupilumab in England (please refer to Document C for

detailed information), the 2022/2023 QOF data were utilised as this represents the most recent estimate of COPD prevalence in England (1,151,474 people).(56) The proposed dupilumab population includes patients who have experienced ≥2 moderate or ≥1 severe exacerbations within the last 12 months despite maximal inhaled therapy (i.e., patients who are uncontrolled). Clinicians we have spoken to, however, highlighted that patients with moderate exacerbations self-medicate using their rescue packs and therefore these moderate exacerbations aren't often reported (outside of clinical trials). We have therefore assumed that a patient is highly unlikely to be identified as a potential dupilumab patient unless they present to the hospital (with either a moderate or severe exacerbation) while being on optimal (triple) inhaled therapy. Therefore, given that moderate exacerbations are poorly defined and vastly underreported by patients in England, we estimate the eligible population as follows:

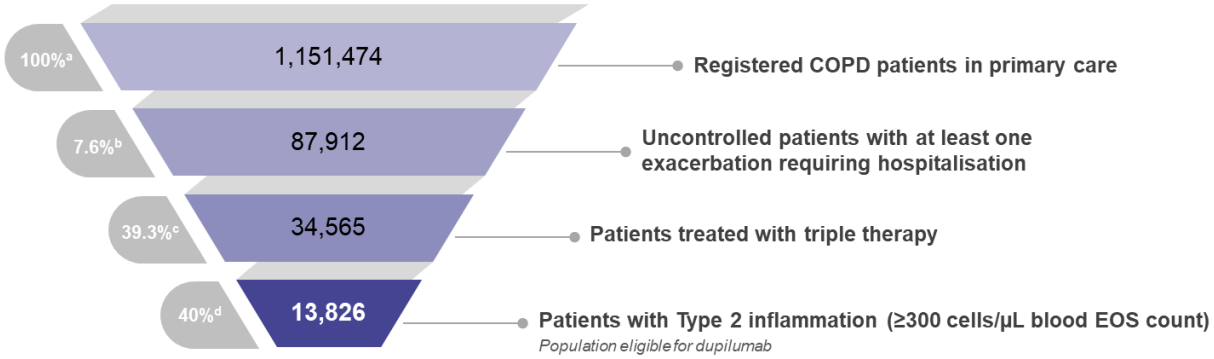
- Based on data from HES England in 2022/23, 7.6% of patients had non-elective hospitalisations, leading to an estimate of 87,912 COPD patients with one or more severe exacerbations.(57)

- Data reported by Whittaker et al. 2022 for patients with COPD aged >40 years registered at general practices in the UK, report that 39.3% of patients with one or more severe exacerbations were already on triple therapy, corresponding to 34,565 patients.(26)

- Finally, it is reported that Type 2 inflammation (≥300 cells/μL blood EOS count) occurs in up to 40% of COPD patients.(46-50)

- This results in a final population of 13,826 patients eligible for treatment with dupilumab (Figure 4).

Figure 4. COPD patient population anticipated to be eligible for treatment with dupilumab in England



COPD = chronic obstructive pulmonary disease
[a]Based on QoF England (2022/2023)(56)
[b]Based on HES England data (2022/2023)(57)
[c]Based on Whittaker et al. 2022(26)
[d]Based on published literature(46-50)

B.1.3.1.3. Morbidity and mortality of COPD

The morbidity and mortality associated with COPD is greater in patients with more severe airflow obstruction (Table 3) and in those who experience exacerbations (as exemplified by patients fitting GOLD group E; Figure 1), as described in the following sections. The humanistic and economic burden of COPD are described in Section B.1.3.1.4 and B.1.3.1.5, respectively.

Mortality

COPD is among the top five leading causes of death in England,(15, 16) accounting for 21,701 deaths per year[iii].(58) Mortality rates for respiratory disease in the UK are among the highest in Europe and were reported to be 61% higher than the European average in 2016.(17)

The prognosis for patients with COPD is poor. In a database study of 339,647 patients with COPD in England between January 2010 and January 2020, 28.8% of patients died during a mean follow-up of 5.5 years, of whom 25.7% died of COPD-related causes (e.g., respiratory failure) and 23.3% died of cardiovascular disease (CVD)-related causes.(30)

A Sanofi-led cohort study used linked, de-identified, routinely collected electronic healthcare record data from CPRD Aurum, HES and the ONS to assess real world clinical outcomes among the dupilumab target population in England.(59) Patients fitting validated COPD criteria who also matched the dupilumab BOREAS trial eligibility criteria as closely as possible (raised EOS ≥300 cells/μL, triple therapy; Section B.2.3.1.1) were followed (N=10,778; 2010 to 2021).(59) Overall, 3,747 patients (34.8%) had uncontrolled disease, defined as ≥2 moderate or ≥1 severe exacerbation in the previous year while receiving triple therapy.(59) In this cohort, 40.62% of patients died during a mean follow-up of 4.1 years, including 601 (39.5%) exacerbation-related deaths, 302 (19.8%) CV-related deaths and 618 (40.6%) deaths due to other causes.(59)

In a national clinical audit of 107,761 adults with COPD admitted to UK hospitals with a COPD exacerbation between 2018 and 2020, 6.1% died within 30 days of admission and 11.9% died within 90 days of admission.(60) Patients aged ≥75 years had a higher risk of 30-day and 90-day mortality than patients aged <65 years.(60) The adjusted odds ratios (ORs) for mortality by sex and age are presented in Table 5.(60)

Table 5. COPD mortality within 30 days and 90 days of hospitalisation in the UK

Variable	Died in 30 days: adjusted OR (95% CI)	Died in 90 days: adjusted OR (95% CI)
Sex		
Men	1 [reference]	1 [reference]
Women	0.88 (0.83, 0.94)	0.87 (0.83, 0.91)
Age		
35-44	0.26 (0.14, 0.48)	0.31 (0.21, 0.47)
45-54	0.38 (0.31, 0.47)	0.43 (0.37, 0.50)

[iii]The number of deaths decreased in 2021 due to the impact of the COVID-19 pandemic. For comparison, 27,195 people died from COPD in 2019.

Variable	Died in 30 days: adjusted OR (95% CI)	Died in 90 days: adjusted OR (95% CI)
55-64	0.64 (0.58, 0.72)	0.64 (0.59, 0.69)
65-74	1 [reference]	1 [reference]
75-84	1.47 (1.37, 1.58)	1.49 (1.41, 1.57)
85+	2.32 (2.13, 2.53)	2.35 (2.20, 2.51)

CI = confidence interval; COPD = chronic obstructive pulmonary disease; OR = odds ratio
Source: Royal College of Physicians 2023(60)

It has been estimated that the life expectancy for current or former smokers with moderate to severe COPD is up to 6 years lower than the general population, in addition to the ~3.5 years lost to smoking.(61) The 2015 NICE quality standards and indicators briefing paper reported that the life expectancy of patients with severe COPD (mean age of death: 74.2 years) is reduced compared to patients with mild disease (mean age of death: 77.2 years) and those who did not have COPD (mean age of death: 78.3 years).(62)

COPD mortality rates are significantly higher in more deprived regions of the UK. According to the INHALE dataset, the 2020 COPD mortality rate in the most deprived decile was 159.4 per 100,000 people compared to 30.9 per 100,000 in the least deprived decile, i.e., over five times higher (approximately 415%). This disparity highlights the substantial impact of socioeconomic factors on health outcomes, particularly for chronic conditions like COPD.(63)

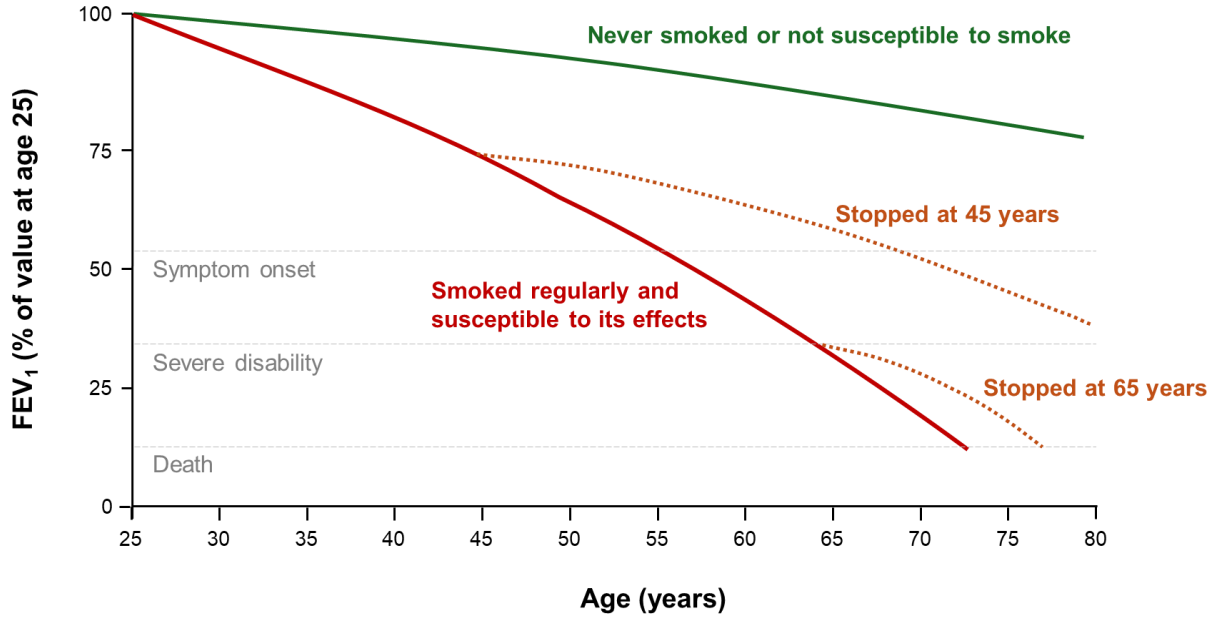
Risk factors for increased mortality among patients with COPD include greater severity of airflow obstruction, higher comorbidity burden, and greater frequency and severity of exacerbations, as detailed in the following sections.(30, 60)

Airflow obstruction

COPD is associated with irreversible and progressive airflow obstruction.(3) Lung function decline is a normal part of the ageing process in adults, but COPD patients have an increased rate of lung function decline over time (Figure 5).(64) Highly accelerated lung function decline is associated with symptoms, exacerbations, respiratory failure and premature death.(64)

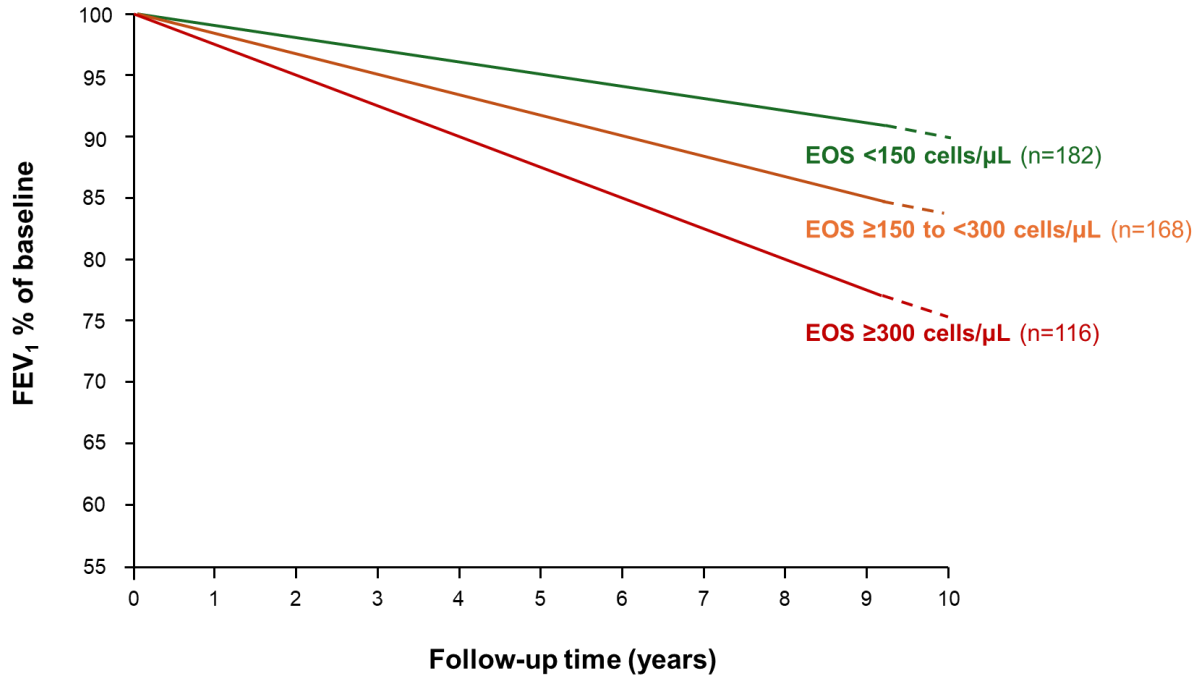
In a 2017 analysis of blood samples from participants in the prospective, population-based Canadian Cohort of Obstructive Lung Disease (CanCOLD) study (N=1,120), high blood EOS levels in patients with COPD were associated with more rapid FEV_1 decline.(41) Patients with blood EOS ≥300 cells/µL had a significantly higher annual rate of FEV_1 decline compared to those with blood EOS <150 cells/µL ($p<0.05$; Figure 6 and Table 6).(41)

Figure 5. Lung function decline in patients with COPD



COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in one second
Source: Adapted from Fletcher and Peto 1977(65)

Figure 6. Lung function decline among patients with COPD by EOS count



The annual decline in FEV_1 among patients with EOS ⩾300 cells/µL was significantly greater than for the those with EOS <150 cells/µL (p=0.0437). No significant difference was seen between the EOS ⩾150 to <300 cells/µL and EOS <150 cells/µL groups (p=0.3265).
COPD = chronic obstructive pulmonary disease; EOS = eosinophil; FEV_1 = forced expiratory volume in one second
Source: Adapted from Tan 2021(41)

Table 6. Rate of FEV_1 decline by blood EOS level in COPD patients

Blood EOS count	n	FEV_1 estimate (mL/year)	Annual rate of change in FEV_1, mL/year (95% CI)
<150 cells/µL	182	Reference	-
≥150 to <300 cells/µL	168	-14.94	−14.94 (−44.84, 14.96)
≥300 cells/µL	116	-34.74	-34.74 (-68.49, -1.00)*

*p<0.05
Note: Data are presented for the mixed effects multivariable regression models for longitudinal lung function decline by thawed blood EOS level of the subgroup with COPD only and no history of doctor diagnosed asthma (N=466; "sensitivity analysis 2 for asthma exclusion")
CI = confidence interval; COPD = chronic obstructive pulmonary disease; EOS = eosinophil; FEV_1 = forced expiratory volume in one second
Source: Tan 2021(41)

In a database study of patients with COPD in England between 2010 and 2020 (N=339,647), increasing severity of airflow obstruction was associated with higher rates of all-cause, COPD-related and CVD-related mortality (Table 7).(30)

Similarly, in an analysis of patients with COPD who participated in the Norwegian Nord-Trøndelag Lung Study (HUNT2) between 1995 and 1997 with follow-up through to 2012 (N=1,540), all-cause mortality was shown to rise with increasing severity of airflow obstruction (Table 8).(66)

Increasing severity of airflow obstruction also leads to greater medical costs and HCRU among patients with COPD, as described in Section B.1.3.1.5.(37, 38)

Table 7. Adjusted mortality rates by FEV_1 % predicted in England

FEV_1 % predicted	Adjusted mortality rates per 1,000 person-years (95% CI)		
	All-cause	COPD-related	CVD-related
≥80%	34.1 (33.5, 34.7)	4.6 (4.4, 4.9)	8.8 (8.4, 9.1)
50%-79%	50.8 (50.2, 51.3)	10.4 (10.2, 10.6)	12.8 (12.5, 13.1)
30%-49%	83.6 (82.4, 84.7)	31.2 (30.5, 31.9)	17.4 (16.9, 18.0)
<30%	144.2 (140.1, 148.3)	84.4 (81.2, 87.6)	21.8 (20.2, 23.4)

Adjusted for age, gender and smoking status.
CI = confidence interval; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; FEV_1 = forced expiratory volume in one second
Source: Whittaker 2024(30)

Table 8. Excess mortality due to COPD severity in Norway

Severity of airflow obstruction	Standardised mortality ratio (95% CI)	
	Males (n=956)	Females (n=584)
FEV_1 ≥80% of predicted	0.91 (0.76, 1.08)	0.75 (0.59, 0.95)
FEV_1 50% to 79% of predicted	1.33 (1.20, 1.47)	1.7 (1.46, 1.99
FEV_1 30 to 49% of predicted	1.77 (1.47, 2.12)	4.72 (3.62, 6.08)
FEV_1 <30% of predicted	3.47 (2.70, 4.39)	5.15 (2.45, 9.92)

CI = confidence interval; COPD = chronic obstructive pulmonary disease
Source: Leivseth et al. 2013(66)

Symptom burden

COPD is associated with persistent respiratory symptoms, including dyspnoea (breathlessness), chronic cough, sputum production, wheezing and chest tightness, as well as systemic effects such as fatigue and weight loss.(3) Symptom burden increases with disease severity, as demonstrated in a cross-sectional study conducted in Spain in 2015 (N=2,669), where patients fitting GOLD groups C and D (per the 2013 GOLD ABCD criteria[iv]; now defined as GOLD group E) experienced greater symptom burden than other GOLD groups as well as a higher impact of COPD symptoms on their HRQoL, daily life and sleep quality.(67)

Higher symptom burden in COPD is associated with an increased risk of exacerbations.(68) In a UK-based cohort of 40,425 COPD patients with dyspnoea identified from the CPRD between April 2009 and March 2011, patients with moderate to severe dyspnoea (Medical Research Council [MRC] ≥3) had a 46% higher risk of exacerbations compared to patients with no dyspnoea, while patients with mild dyspnoea (MRC 2) experienced an 18% higher risk of exacerbations.(68)

COPD symptoms have a substantial negative impact on patient's health status, daily activities and overall wellbeing (as described in Section B.1.3.1.4) and also contribute to the substantial medical costs and HCRU associated with the disease (as described in Section B.1.3.1.5).

Comorbidities

COPD is associated with both airway and systemic inflammation (Section B.1.3.1.1), which may adversely affect the functioning of extrapulmonary systems, increasing the likelihood of comorbid cardiovascular, neurological, gastrointestinal, metabolic and non-COPD respiratory diseases.(3) Complications often associated with COPD are summarised in the recently updated NICE Clinical Knowledge Summary for COPD, highlighting depression and anxiety, cor pulmonale, chest infections, secondary polycythaemia, respiratory failure, pneumothorax, lung cancer, and muscle wasting and cachexia.(69)

A cross-sectional study of UK primary care data from 314 Scottish practices (2007; N=1,272,685; n=51,928 with COPD) found that 86% of patients with COPD had ≥1 comorbidity compared to 48.9% of those without COPD. A total of 22.3% of patients with COPD had ≥5 comorbidities compared to 4.9% of those without COPD (adjusted OR: 2.63; 95% CI: 2.56, 2.70).(70)

The Spanish observational CLAVE study (2017 to 2018; N=4,801) recently reported that the most frequent comorbidities in patients with severe COPD (FEV_1 <50% of predicted) were:

[iv] 2013 classification; GOLD A: mMRC 0-1 and CAT <10, GOLD 1 or 2, 0-1 exacerbations (not leading to hospitalisation); GOLD B: mMRC ≥2 or CAT ≥10, GOLD 1 or 2, 0-1 exacerbations (not leading to hospitalisation); GOLD C: mMRC 0-1 and CAT <10, GOLD 3 or 4, ≥2 or ≥1 exacerbations (leading to hospitalisation); GOLD D: mMRC ≥2 or CAT ≥10, GOLD 3 or 4, ≥2 or ≥1 exacerbations (leading to hospitalisation)

- Metabolic disorders (arterial hypertension [51.2%], dyslipidaemia [36.0%], diabetes mellitus [24.9%], abdominal obesity [15.8%])
- Cardiovascular diseases (myocardial infarction [10.1%], heart failure [11.6%], peripheral vascular disease [10.4%], atrial fibrillation [11.5%]), and
- Psychological disorders (anxiety [14.1%], depression [11.8%]).(71)

The presence of these comorbidities adversely impacts patient COPD outcomes and quality of life. Comorbidities are associated with an increased risk of mortality in patients with COPD.(60) Among 107,761 adults with COPD admitted to UK hospitals with a COPD exacerbation between 2018 and 2020, patients with a higher comorbidity burden (as measured by the Charlson comorbidity index[v](72)) had an increased risk of 30-day and 90-day mortality than patients with a lower comorbidity burden (Table 9).(60)

Table 9. COPD mortality within 30 days and 90 days of hospitalisation in the UK, stratified by Charlson comorbidity index

Charlson comorbidity index	Died in 30 days: adjusted OR (95% CI)	Died in 90 days: adjusted OR (95% CI)
0-1	1	1
2	1.14 (1.03, 1.27)	1.21 (1.12, 1.31)
3	1.57 (1.46, 1.69)	1.71 (1.62, 1.80)
4	1.88 (1.68, 2.09)	1.97 (1.81, 2.14)
5	2.07 (1.78, 2.40)	2.40 (2.15, 2.68)
6	2.81 (2.26, 3.49)	2.55 (2.13, 3.05)
7+	5.29 (4.56, 6.14)	6.38 (5.65, 7.21)

CI = confidence interval; OR = odds ratio
Source: Royal College of Physicians 2023(60)

The estimated annual frequency of adverse events in patients with COPD in the UK in 2022, potentially attributable to comorbid disease is presented in Table 10, based on a 2023 report by Asthma and Lung UK.(36) The most common adverse events were estimated to be atrial flutter, constipation and heart failure.(36)

Table 10. Annual frequency of adverse events associated with COPD, by descending frequency

Adverse effect	Annual frequency
Atrial flutter	0.335
Constipation	0.0551
Heart failure	0.0464
Diarrhoea	0.0266
Angina	0.0167
Syncope	0.0153
Pneumonia	0.0148

[v] The Charlson comorbidity index (CCI) assesses comorbidity level by taking into account both the number and severity of 19 pre-defined comorbid conditions. The total score in the CCI is derived by summing the assigned weights of all comorbid conditions presented. Higher scores indicate a more severe condition and consequently, a worse prognosis.

Adverse effect	Annual frequency
Stroke	0.0122
Urinary retention	0.0109
Myocardial infarction	0.01
Dry mouth	0.003
Cardiac arrest	0.0017
Glaucoma	0.0015
Ventricular tachycardia	0.0004

COPD = chronic obstructive pulmonary disease
Source: Asthma and Lung UK 2023(36)

Major adverse cardiovascular events (MACE)

Patients with COPD are two to five times more likely than the general population to develop CVD, an association that can be partly attributed to commonalities in risk factors such as exposure to cigarette smoke.(73, 74) Comorbid CVD worsens the prognosis of COPD, being associated with an increased severity of COPD exacerbations, an increased risk of CV events, frequent hospitalisation and death in approximately 20% of COPD patients.(73, 75)

In the Sanofi-led HES-CPRD study described previously (N=10,778; 2010 to 2021), 16.84% (n=631) of patients with uncontrolled COPD experienced a first MACE during follow-up, of which 29% were fatal.(59)

Cardiovascular complications are particularly common following a COPD exacerbation, as described in the following section.(29)

Exacerbations

COPD exacerbations are acute episodes of symptom worsening, associated with increased airway/systemic inflammation and physiological changes.(76) The severity of exacerbations varies and is classified based on the type of treatment required, increasing from mild (requiring short-acting bronchodilators only), through moderate (requiring short-acting bronchodilators and OCS ± antibiotics) to severe (requiring hospitalisation or ED consultation), as summarised in Section B.1.3.1.(3)

Moderate Exacerbations

In England, NICE advocates for the use of rescue packs[vi] to facilitate prompt treatment of moderate exacerbations and minimise the risk of complications; however, they impose significant clinical burdens and there use relies on ongoing monitoring and education to help prevent overuse of antibiotics and systemic corticosteroids.(7)

[vi] A COPD rescue pack consists of a short course of steroids and antibiotics prescribed by a doctor in advance and kept in the patients home for use in case of exacerbations.

Oral Corticosteroids

Short courses of oral corticosteroids, such as prednisone, are commonly used to reduce airway inflammation and improve lung function during COPD exacerbations. Despite their benefits, corticosteroids are associated with several adverse effects that contribute to the clinical burden for these patients.

One of the most significant concerns is the increased risk of pneumonia. Oral corticosteroids suppress the immune response, which has been shown to elevate the incidence of pneumonia in COPD patients.(77) Additionally, the long-term consequences of recurrent corticosteroid use, even in short bursts, include osteoporosis and an increased risk of fractures.(78)

The adverse effects of oral corticosteroids can be particularly detrimental for COPD patients, who often suffer from other comorbid chronic conditions such as heart failure, diabetes mellitus, and muscle weakness.(77, 79, 80) These risks necessitate regular monitoring and management of cardiovascular comorbidities, further burdening both patients and healthcare systems.

Antibiotics

The use of antibiotics during moderate COPD exacerbations aims to control bacterial infections that may exacerbate symptoms. However, the widespread use of antibiotics in this population, even in short courses, presents several clinical challenges.

A major concern is the development of antibiotic resistance. COPD patients frequently require repeated courses of antibiotics due to recurrent exacerbations, increasing the likelihood of bacterial resistance.(81, 82) Additionally, antibiotic resistance may necessitate patients returning to provide sputum samples for culture and sensitivity testing, prolonging the treatment process and increasing the burden on both patients and healthcare resources.(83) This issue is underscored by the specific NICE guideline (NG114) on antimicrobial prescribing in COPD for acute exacerbations.

An experienced clinical expert, a respiratory nurse specialist, highlighted the clinical burden from adverse events related to rescue packs and the common frequency of alternative antibiotic prescribing due to resistance and the need for sputum sampling.(84)

Despite treatment with triple therapy, almost two-thirds of patients with COPD in the UK continue to experience moderate or severe exacerbations.(26, 40) In 2023, it was estimated that 4,476,940 moderate exacerbations and 400,291 severe exacerbations occurred in patients with COPD in England.(36)

Severe exacerbations

A severe exacerbation is an intense worsening of symptoms, requiring hospitalisation. A Sanofi-led analysis using HES data evaluated the resource use associated with severe COPD exacerbations in

England between April 2018 and February 2024 (N=357,410; see Appendix M for study details). On average, a severe exacerbation includes a length of stay of 2.9 days, 88% of spells were admitted via A&E and 14% of spells were associated with a readmission within 30 days.

COPD exacerbations and Type 2 inflammation

In the Sanofi-led HES-CPRD study described previously (N=10,778; 2010 to 2021), involving uncontrolled COPD (≥2 moderate or ≥1 severe historical exacerbations within 12 months) with Type 2 inflammation (blood EOS ≥300 cells/μL) treated with triple therapy, 3,747 patients (34.8%) had uncontrolled disease, defined as ≥2 moderate or ≥1 severe exacerbation in the previous year while receiving triple therapy.(59) Patients with uncontrolled COPD experienced a median of 6 moderate or severe exacerbations during the study period, with a mean annual rate of 2.294 moderate (95% CI: 2.676, 2.729), 0.408 severe (0.398, 0.418) and 0.039 fatal (0.036, 0.418) exacerbations.(59)

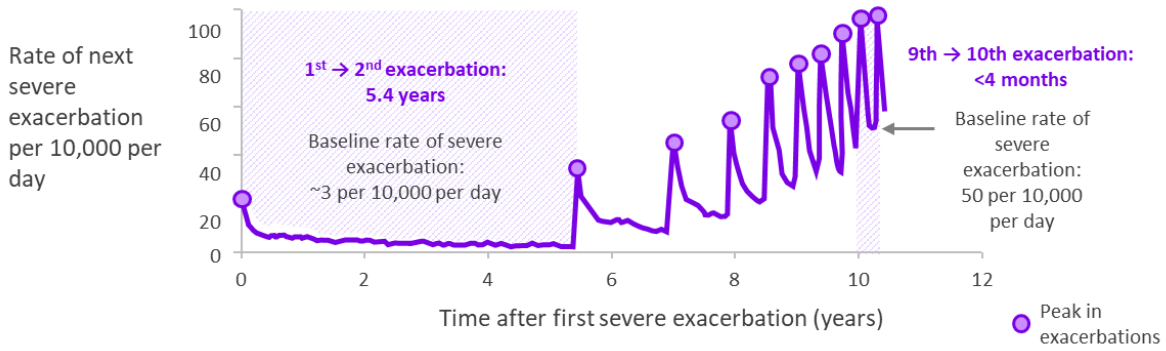
The risk of exacerbations is higher in patients with COPD and Type 2 inflammation. A study conducted in Spain between March 2016 and January 2018 (N=322) found that patients with COPD and Type 2 biomarkers (raised blood EOS, high FeNO) had a significantly increased risk of moderate or severe exacerbation during the one year follow-up period than those without Type 2 biomarkers (HR: 1.73; 95% CI: 1.26, 2.28; p=0.001).(42) Patients with Type 2 biomarkers also had a significantly shorter time to first moderate or severe COPD exacerbation compared to those without Type 2 biomarkers (240 days vs. 317 days, respectively; p<0.05).(42)

Impact of COPD Exacerbations

Critically, it is important to recognise that COPD exacerbations are associated with an increased risk of future exacerbations, lung damage and decreased lung function, higher symptom burden, increased risk of CV events and greater risk of death; severe COPD exacerbations are associated with greater morbidity and mortality than moderate exacerbations. Consequently, exacerbations can be considered “sentinel” events for this progressive disease.

- **Increased risk of subsequent exacerbations**
    - In a Danish study (2008–2014) of 8,453 patients in GOLD group B, one moderate exacerbation increased the OR of experiencing a new moderate exacerbation by 1.58 (95% CI: 1.33, 1.87) while ≥2 moderate exacerbations increased the OR by 2.60 (95% CI: 2.19, 3.08) compared to patients with no exacerbations in the previous year.(85)
    - Similarly, a Canadian study (N=73,106; 1990–2005) found that the risk of subsequent COPD exacerbations increased with each successive severe exacerbation (adjusted hazard ratio [HR] for second successive exacerbation: 1.76; adjusted HR for tenth or greater successive exacerbation: 5.21), and that the median time between exacerbations reduced from approximately 5 years after the first hospitalised exacerbation, to 4 months after the 9th (Figure 7).(27)

Figure 7. Increasing frequency of severe exacerbations among patients with COPD



Source: Adapted from Suissa 2012(27)

- **Higher symptom burden**
  - A global meta-analysis of 18,746 patients with COPD from seven RCTs identified a significant worsening in symptom burden (as measured by CAT score) of 0.85 points (95% CI: 0.77, 0.92) with each moderate exacerbation event.(28)
- **Increased risk of CV events**
  - A global systematic review and meta-analysis (2000–2021; n=7 studies) found a significantly increased risk of acute myocardial infarction (risk ratio [RR]: 2.43) and stroke (RR: 1.68) in the 1-3 months after a moderate or severe COPD exacerbation.(29)
  - A post-hoc analysis of the SUMMIT RCT (N=16,485) demonstrated that the risk of CV events was 4-fold higher following an exacerbation (any severity) and 10-fold higher following a severe exacerbation, and the risk of CV events remains elevated for up to a year (Table 11).(86)
  - A retrospective cohort study of patients with newly diagnosed COPD in the US (2012–2019; N=435,925) found that the risk of CV events following an exacerbation was highest during the first 30 days, but increased risk persisted for 1 year.(87)

Table 11. Risk of CV events following a COPD exacerbation

Period	Number of participants in period	Number of participants with an adjudicated CV event	HR (95% CI)
Any exacerbation			
Baseline	16,477	487	Reference
1 to 30 days post-exacerbation	4,639	32	3.8 (2.7, 5.5)
31 days to 90 days post-exacerbation	4,235	29	1.9 (1.3, 2.7)
91 days to 1 year post-exacerbation	3,779	91	1.9 (1.5, 2.4)
>1 year post-exacerbation	2,179	41	1.2 (0.8, 1.7)
Severe exacerbation			
Baseline	16,476	605	Reference
1 to 30 days post-exacerbation	1,243	24	9.9 (6.6–14.9)
31 days to 90 days post-exacerbation	998	15	3.7 (2.2–6.1)

Period	Number of participants in period	Number of participants with an adjudicated CV event	HR (95% CI)
91 days to 1 year post-exacerbation	862	24	2.0 (1.3–3.0)
>1 year post-exacerbation	447	11	1.3 (0.7–2.6)

CI = confidence interval; CV = cardiovascular event; HR = hazard ratio
Source: Kunisaki et al. 2018(86)

- **Greater risk of death**
    - In a database study of 339,647 patients with COPD in England between January 2010 and January 2020, adjusted all-cause mortality and COPD-related mortality were higher in patients with any exacerbation compared to patients with no baseline exacerbations (Table 12).(30) Furthermore, mortality was higher in patients with a greater frequency of exacerbations and patients with severe exacerbations versus moderate exacerbations.(30)

Table 12. Adjusted mortality rates by number and severity of exacerbations in England

Variable	Adjusted mortality rates per 1,000 person-years (95% CI)		
	All-cause	COPD-related	CVD-related
Exacerbations (any vs none)			
None	53.4 (53.1, 53.4)	12.2 (12.0, 12.4)	13.1 (12.9, 13.4)
Any	71.1 (70.4, 71.2)	21.7 (21.3, 22.1)	15.9 (15.5, 16.2)
Exacerbation frequency			
None	53.4 (53.1, 54.0)	12.2 (12.0, 12.4)	13.1 (12.9, 13.4)
<2	64.6 (63.8, 65.5)	18.2 (17.8, 18.7)	14.8 (14.3, 15.2)
2+	83.1 (81.8, 84.5)	28.0 (27.2, 28.9)	17.9 (17.3, 18.6)
Exacerbation severity			
None	53.4 (53.1, 53.4)	12.2 (12.0, 12.4)	13.1 (12.9, 13.4)
Moderate	66.6 (65.9, 67.4)	19.1 (18.7, 19.6)	15.1 (14.7, 15.4)
Severe	125.0 (122.1, 128.0)	47.4 (45.5, 49.2)	26.3 (24.9, 27.6)

CI = confidence interval; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease
Source: Whittaker 2023(30)

COPD exacerbations have a substantial negative impact on patient's daily activities and overall HRQoL (as described in Section B.1.3.1.4) and also contribute to the substantial medical costs and HCRU associated with the disease (as described in Section B.1.3.1.5).

Patients with COPD living in deprived areas are more likely to experience frequent exacerbations. Key factors include low household income, poor housing conditions (cold and damp) and higher smoking rates.(88) These socioeconomic factors significantly contribute to the increased burden of COPD in these populations, such as an increased level of exacerbations. The findings highlight the need for targeted interventions to address these disparities and improve COPD outcomes.(88)

B.1.3.1.4. Humanistic burden of COPD

Impact on patients

Market research conducted by Sanofi in August 2023 among patients (n=8) and clinicians (n=12) in the UK reinforces that COPD is a condition characterised by despair.(33) Most patients surveyed had been hospitalised at least once, and all but one were using triple therapy.(33) All patients surveyed were regularly using oral steroids and/or antibiotics to manage exacerbations.(33)

In the survey, patients reported that COPD feels like a very frightening, long, protracted death sentence which they have brought upon themselves.(33) This leads to shame and stigma, and impacts hugely on every aspect of their life.(33) For many, life feels extremely limited and they are frequently confined to their homes.(33) Patients feel there is little that can be done to improve their HRQoL.(33) One patient surveyed said *"There's nothing they can give me. I'm basically stuck with it….I just have to live with it, it's just the way it is".(33)* The clinicians surveyed also recognised that there is little they can achieve as current treatments, which have remained relatively unchanged over the past decades, have limited impact.(33) Their main goal is to stabilise the patient's condition, which will ultimately progress, placing an emotional burden on healthcare professionals (HCPs).(33) The clinicians surveyed reported that they find it difficult, if not impossible, to break the cycle of exacerbations and associated hospitalisations for some patients and this can ultimately lead to a sense of failure.(33) A respiratory specialist stated that *"The despair is the patient's, but also that translates to the doctor. It's not curable and they endlessly come back …(and) there is only so much we can do".*(33)

Symptoms

COPD symptoms, particularly dyspnoea, have a substantial negative impact on health status, daily activities and overall wellbeing.(89) Without effective treatment, health status declines with disease progression over time, often referred to as the "spiral of decline".(90)

Dyspnoea also limits physical exertion and affects patients' ability to perform routine tasks.(89) COPD symptoms, such as coughing and dyspnoea, influence the patient's quality of sleep, which may increase symptoms of fatigue, anxiety and depression, thereby further affecting their HRQoL.(89) In a telephone survey that screened 83,592 households in France, Italy, Germany, Spain, the UK and the US and identified 1,107 patients with COPD, symptoms such as increased sputum production (35%), coughing (42%), fatigue (37%) and dyspnoea (37%) were most cited as impacting patient's wellbeing.(91)

A study analysing data from the 5-European Union (EU) 2013 National Health and Wellness Survey in adults aged ≥40 years with COPD (N=768), which included 180 participants from the UK, reported that patients with more severe dyspnoea (mMRC score ≥2) had significantly worse HRQoL as measured by the Short Form-36 (SF-36) health questionnaire compared to those with less severe dyspnoea (mMRC score <2; p<0.001).(34)

Exacerbations

COPD exacerbations are also associated with poor HRQoL. A globally focussed systematic literature review identified clinical studies published up to October 2019 in which the HRQoL of patients with COPD and exacerbations was evaluated.(28) Meta-analysis of data from seven RCTs (representing data from 18,746 patients) demonstrated an increase in total SGRQ score from baseline of 1.88 (95% CI: 1.72, 2.04) per moderate COPD exacerbation and 2.92 (95% CI: 2.48, 3.36) per severe exacerbation.(28) Further, an increase in the rate of exacerbations by one moderate event per year led to a reduction in EQ-5D-5L score of −0.02 (95% CI: −0.02, −0.01) from baseline, while one additional severe event per year led to a reduction of −0.03 (95% CI: −0.04, −0.02) from baseline.(28)

Severe exacerbations also have a devastating impact on physical activity levels, skeletal muscle function and exercise tolerance.(92) For example:

- In a multicentre study of outpatients with moderate or severe COPD conducted in Spain (N=441), 45% of patients reported becoming bed- or couch-bound after a community-treated exacerbation, and 55% reported having to stop work.(93)
- In a multinational interview-based survey of patients with predominantly moderate to very severe COPD and ≥2 exacerbations during the previous year (N=125), 86% of patients reported that an exacerbations had a significant impact on their activities of daily living, with 47% stopping all activities completely.(94)
- In a systematic review of 217 relevant quantitative studies, patients with COPD rated exacerbations as the most important outcome.(95) For moderate exacerbations, patients will experience mild-to-moderate worsening of breathlessness and cough, and the symptoms interfere with daily activities; while patients with a severe exacerbation will experience severe-to-very severe worsening of breathlessness and cough, and the symptoms will completely disrupt daily activities.

Anxiety and depression

Patients in the UK surveyed by Sanofi reported anxiety and depression due to COPD.(33) Anxiety and depression occur more frequently in patients with COPD than in patients with other chronic diseases such as hypertension, diabetes, cancer or musculoskeletal disorders(96-98) and are much more prevalent among patients with COPD than in the general population.(97, 99-101)

A summary of international studies found that the prevalence of depression has been reported to range from 10% to 42% in patients with stable COPD.(97) In a systematic review, the prevalence of depression in patients hospitalised for COPD exacerbations ranged from 10% to 86%, depending on the methods used for the diagnosis and assessment of depression.(102) In a UK database study that followed up on patients who were first diagnosed with COPD between January 1995 and December 2005, patients with severe COPD requiring oxygen had the highest relative risk of developing

depression (OR: 2.01; 95% CI: 1.45, 2.78) compared with patients with moderate (OR: 1.44; 95% CI: 1.29, 1.61) or mild COPD (OR: 1.19; 95% CI: 0.92, 1.54).(103)

Patients with COPD are also more likely to develop anxiety compared to matched controls (adjusted OR: 1.85; 95% CI: 1.072, 3.18) and the prevalence of panic disorders may be up to 10-fold higher than in the general population.(100, 104) Clinical anxiety (including generalised anxiety disorder, panic disorders and specific phobias) in COPD has been reported to occur in 13% to 46% of outpatients and 10% to 55% of inpatients.(105)

In a 2014 pan-European observational study of adults aged ≥40 years with stable COPD (N=727), which included clinical practice centres in the UK, patients with more persistent respiratory symptoms were reported to have higher levels of anxiety, depression and poor sleep quality.(106)

Depression and anxiety often occur concurrently in COPD, with the proportion of patients reporting both conditions ranging from 26% to 43%.(107, 108) Patients with COPD who meet the criteria for both depression and anxiety are at a heightened risk of suicidal ideation, increased physical disability and chronic depressive symptoms versus those with either disorder alone.(105, 109)

The relationship between depression/anxiety and COPD is complex and bidirectional.(110) While COPD itself increases the risk of experiencing depression and anxiety, examples from the literature demonstrate that depression and anxiety also have negative impacts on multiple COPD outcomes:

- **Increased mortality risk:** Depression and anxiety may contribute to poor self-care, reduced physical activity and non-adherence to treatment plans, ultimately affecting survival rates in COPD.(110, 111)
- **Worse COPD symptoms:** Depression exacerbates COPD symptoms such as dyspnoea.(112)
- **Increased risk of exacerbations:** Depression and anxiety increase the risk of moderate and severe COPD exacerbations.(113)
- **Reduced HRQoL:** Depression and anxiety affect a person's overall wellbeing, leading to decreased HRQoL in patients with COPD.(114) They amplify feelings of fatigue, hopelessness and social isolation, making it harder to cope with COPD symptoms.(96, 115)
- **Greater healthcare utilisation and costs:** Depression in patients with COPD is associated with increased HCRU, including higher numbers of hospitalisations and emergency room visits as well as longer hospital stays.(111, 116, 117)

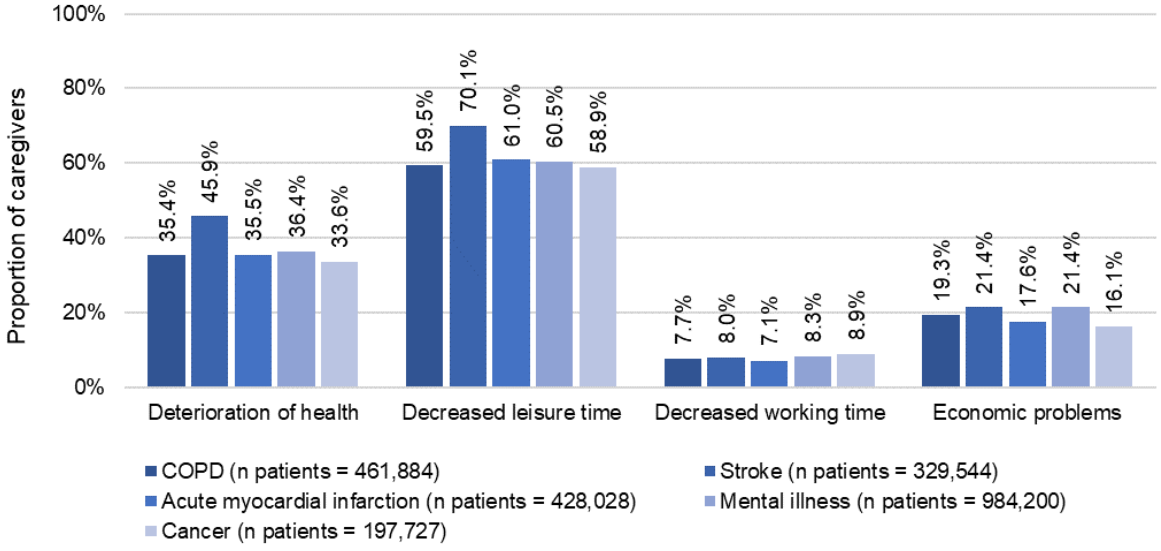
Physical impairments

A 2017 US cross-sectional survey (N=1,775) found that patients fitting GOLD group C and D criteria (per the 2013 GOLD ABCD criteria[vii]; now defined as GOLD group E) experienced the greatest physical impairment with a combined mean Functional Performance Inventory-Short Form (FPI-SF) total score of 1.9, compared with scores of 2.6 and 2.1 for patients in GOLD groups A and B, respectively.(118) Increased physical impairment may result in an increased caregiver burden and further impact all aspects of a patient's HRQoL.

Impact on caregivers

The majority (71%) of patients with COPD require informal caregiver support;(119) caregivers are often physically, emotionally and financially impacted, which may have significant negative effects on their daily lives.(35) For example, a Spanish study analysed 220,892 informal caregivers of patients with COPD and found that 83% had leisure/social-related problems, 38% had professional-related problems (among those of working age, <65 years old) and 35% had health-related problems due to their caregiving.(35) Individuals who provide informal care to patients with COPD experience a level of burden similar to that of caregivers of patients with other chronic diseases, such as stroke or cancer (Figure 8).(35)

Figure 8. Proportion of informal caregivers of COPD patients having problems vs. caregivers of patients with other chronic diseases



COPD = chronic obstructive pulmonary disease
Source: Miravitlles 2015(35)

[vii] 2013 classification; GOLD A: mMRC 0-1 and CAT <10, GOLD 1 or 2, 0-1 exacerbations (not leading to hospitalisation); GOLD B: mMRC ≥2 or CAT ≥10, GOLD 1 or 2, 0-1 exacerbations (not leading to hospitalisation); GOLD C: mMRC 0-1 and CAT <10, GOLD 3 or 4, ≥2 or ≥1 exacerbations (leading to hospitalisation); GOLD D: mMRC ≥2 or CAT ≥10, GOLD 3 or 4, ≥2 or ≥1 exacerbations (leading to hospitalisation)

B.1.3.1.5. Economic burden of COPD

COPD is associated with considerable HCRU and associated costs, largely driven by exacerbations, as well as high indirect costs due to absenteeism, reduced productivity and early retirement among patients and caregivers. For example, COPD is the second largest cause of emergency admissions (around 130,000 per year), and accounts for around 1.4 million GP consultations per year.(120) A cost of illness model developed by Asthma and Lung UK estimated that the total cost of COPD in the UK, including both direct and indirect costs, was £9 billion in 2023.(36) For comparison, the total cost of lung cancer in the UK is estimated at £2.4 billion annually.(121, 122)

Direct costs and healthcare resource use

COPD is associated with substantial medical costs and HCRU, which increase as a function of disease severity (airflow obstruction, symptom burden and exacerbations).(37, 38)

Based on the cost of illness model developed by Asthma and Lung UK, the direct costs of COPD in England were estimated to be £3.9 billion in 2023.(36) Of the direct costs assessed, exacerbation costs accounted for the largest proportion (£1.4 billion), followed by maintenance costs (defined as routine healthcare resources used for COPD[viii]; £0.9 billion), adverse effect costs (defined as negative health events[ix] associated with COPD; £0.9 billion) and treatment costs (£0.7 billion; Figure 9).(36) Annual maintenance costs for 2022, categorised by GOLD group (based on the GOLD 2020 ABCD classification[x]), demonstrated higher costs among patients with more severe disease (symptom burden and exacerbations), ranging from £109 for patients in GOLD A, £118 for GOLD B, £796 for GOLD C and £1,474 for GOLD D.(36)

Figure 9. Direct costs of COPD in England in 2023

COPD = chronic obstructive pulmonary disease
Source: Asthma and Lung UK, 2023(36)

[viii] GP visits; respiratory team visits; outpatient visits; spirometry; pulmonary rehabilitation; home oxygen therapy; influenza vaccine; SAMA; SABA; theophylline; mucolytics; oral corticosteroids; CT scan
[ix] Cardiac arrest; syncope; ventricular tachycardia; myocardial infarction; atrial fibrillation/flutter; angina; stroke; heart failure; pneumonia; constipation; diarrhoea; dry mouth; urinary retention; glaucoma
[x] 2020 classification; GOLD A: mMRC 0-1 or CAT <10, 0-1 exacerbations (not leading to hospitalisation); GOLD B: mMRC ≥2 or CAT ≥10, 0-1 exacerbations (not leading to hospitalisation); GOLD C: mMRC 0-1 or CAT <10, ≥2 exacerbations (not leading to hospitalisation) or ≥1 exacerbation (leading to hospitalisation); GOLD D: mMRC ≥2 or CAT ≥10, ≥2 exacerbations (not leading to hospitalisation) or ≥1 exacerbation (leading to hospitalisation)

A retrospective cohort study analysing data from patients with COPD (N=7,881) diagnosed between 2008 and 2009 in the UK reported annual COPD management costs per patient per year (excluding medication costs; cost year: 2011) of £2,047 in the 24 months following COPD diagnosis.(37) The majority of these costs were attributed to general practitioner (GP) visits (58.5%), followed by non-COPD hospitalisations (31.4%) and exacerbations (10.2%).(37) Annual COPD management costs rose with increasing severity of airflow obstruction, with patients with mild, moderate, severe or very severe airflow obstruction (as defined in Table 3) incurring costs of £1,921, £2,046, £2,092 and £2,293 per patient per year, respectively.(37)

In a retrospective longitudinal analysis, data from CPRD linked to HES in England were used to assess HCRU in a cohort of patients with COPD (N=44,201) from 2011 to 2013.(38) The study found that patients in higher GOLD groups (as per the 2013 GOLD ABCD criteria[xi]) was associated with an increased frequency of GP visits, ranging from 4.72 per person-year for patients in GOLD A to 6.91 per PY for patients in GOLD D (Table 13).(38) In addition, patients with more severe symptoms, categorised as GOLD B or D, had the highest annual rates of COPD-related hospital admissions, at 0.57 and 0.85 per PY, respectively, compared to patients in GOLD A or C.(38)

Table 13. Annual HCRU per person-year in patients with COPD by GOLD group in England in 2013

GOLD category*	Total person-years at risk	COPD-related hospitalisations (rate of admissions [95% CI])	Non-COPD hospitalisations (rate of admissions [95% CI])	GP visits (rate of visits [95% CI])
GOLD A	8,957.15	0.35 (0.31, 0.40)	0.39 (0.37, 0.40)	4.72 (4.62, 4.84)
GOLD B	4,888.70	0.57 (0.54, 0.61)	0.42 (0.41, 0.44)	5.71 (5.54, 5.89)
GOLD C	4,580.30	0.44 (0.40, 0.48)	0.32 (0.30, 0.34)	6.09 (5.93, 6.28)
GOLD D	5,945.35	0.85 (0.81, 0.89)	0.28 (0.27, 0.30)	6.91 (6.75, 7.10)

*GOLD 2013 classification
CI = confidence interval; COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; GP = general practitioner; HCRU = healthcare resource use
Source: Merinopoulou, 2016(38)

A Sanofi-led analysis using HES data evaluated the resource use associated with severe COPD exacerbations in England between April 2018 and February 2024 (N=357,410; see Appendix M for study details).(123) For the purposes of this analysis, a severe exacerbation was defined as one requiring a hospital stay.(123) The resource use associated with each severe exacerbation is summarised in Table 14.(123)

[xi] 2013 classification; GOLD A: mMRC 0-1 and CAT <10, GOLD 1 or 2, 0-1 exacerbations (not leading to hospitalisation); GOLD B: mMRC ≥2 or CAT ≥10, GOLD 1 or 2, 0-1 exacerbations (not leading to hospitalisation); GOLD C: mMRC 0-1 and CAT <10, GOLD 3 or 4, ≥2 or ≥1 exacerbations (leading to hospitalisation); GOLD D: mMRC ≥2 or CAT ≥10, GOLD 3 or 4, ≥2 or ≥1 exacerbations (leading to hospitalisation)

Table 14. HCRU associated with severe exacerbations in England between 2018 and 2024

Resources	Frequency per exacerbation
Ambulance transport	0.7
A&E admission	0.88
Hospital stay (LOS)	2.9 days
ICU (LOS)	0.01 days
Readmission within 30 days	0.14
Ventilation	0.07
Oxygen therapy	0.02
CT scan	0.1
Echocardiogram	0.05
CPAP therapy	0.01
Follow-up outpatient appointments within 30 days of exacerbation	0.18
Follow-up outpatient appointments within 90 days of exacerbation	0.37

A&E = accident and emergency; CPAP = continuous positive airway pressure; CT = computed tomography; HCRU = healthcare resource use; HES = Hospital Episode Statistics; ICU = intensive care unit; LOS = length of stay
Source: Sanofi 2024 [Data on file] HES 2018-2024(123)

Hospital readmissions are common among patients with COPD. The 2023 summary report published by the National Asthma and COPD Disease Audit Programme (NACAP) of the Royal College of Physicians reports that 24.4% and 43.1% of patients with COPD were readmitted within 30 and 90 days after discharge, respectively.(124)

A multi-country trial on the burden of COPD highlighted significant seasonal variations in COPD exacerbations and deaths, with peaks in winter and declines in summer.(125) These fluctuations lead to high opportunity costs in secondary care due to increased bed occupancy during peak periods, straining healthcare resources and delaying care for other patients.(125) The problem is exacerbated by the need to allocate more resources during winter, impacting hospital efficiency and financial performance.(125) Interventions that reduce exacerbations can help mitigate these opportunity costs, ensuring better resource management and patient care.(125)

Data from outside of the UK indicate that patients with COPD and Type 2 inflammation have a higher economic burden than those without Type 2 inflammation.(126, 127) A cross-sectional US study (2011–2015) of patients with COPD (N=2,832; cost year: 2016) showed that patients with blood EOS counts ≥150 cells/μL incurred significantly higher COPD-related healthcare costs (USD$9,800 difference; p=0.006) and total healthcare costs (USD$14,412 difference; p=0.002) than patients with blood EOS counts <150 cells/μL.(126) Furthermore, in a retrospective Canadian study (2006–2013) of patients with COPD (N=479), eosinophilic patients (≥200 cells/μL or ≥2% of total white blood cells) had a significantly increased risk of 1-year COPD-related readmission (OR: 1.83; p=0.009), shorter time to first COPD-related readmission (HR: 1.64; p=0.007) and higher number of 1-year COPD-related emergency department visits (IRR: 1.78; p=0.003) compared to non-eosinophilic patients.(127)

Indirect costs

COPD drives indirect costs due to premature death (Section B.1.3.1.3), limitation of physical activities (Section B.1.3.1.4) and missed work time for both patients and caregivers. The Continuing to Confront COPD International Patient Survey, which was conducted between 2012 and 2013 and included 305 patients with COPD from the UK, found that 70% of patients in the UK experienced a negative impact on their work.(128) Specifically, 52% of patients reported being completely unable to work, while 18% reported having a reduced ability to work.(128)

Patients with COPD may have to retire earlier than members of the workforce without COPD.(39) In an analysis of German electronic health records for patients with COPD and matched controls between September 2010 and December 2013 (COSYCONET), COPD was significantly associated with early retirement (Table 15).(129) Early retirement was identified as a major driver of indirect costs in patients with COPD.(129)

Table 15. Early retirement among patients with COPD in Germany

	FEV_1 ≥80% of predicted (n=72)	**FEV_1 50% to 79% of predicted (n=377)**	**FEV_1 30 to 49% of predicted (n=352)**	**FEV_1 <30% of predicted (n=133)**	**Control (n=856)**	**p-value**
Proportion with early retirement (%)	34.7	36.6	51.4	72.2	14.7	<0.0001
Costs associated with early retirement (2012€)	€12,891	€13,590	€19,090	€26,798	€5,465	<0.0001

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in the first second
Source: Wacker 2016(129)

A Spanish study investigating the burden faced by informal caregivers of patients with COPD (N=220,892) found that 37.3% of caregivers under the age of 65 experienced work-related problems.(35) The most frequently reported work-related problems were the inability to work outside the home (22.7%), economic problems (19.3%) and the need to stop working altogether (11.5%).(35)

Based on the cost of illness model developed by Asthma and Lung UK, the total productivity costs of COPD in England were estimated to be £1.7 billion in 2023.(36) In addition, the total costs associated with quality-adjusted life years (QALY) losses due to moderate/severe exacerbations and adverse effects of COPD were estimated to be £2.3 billion.(36)

B.1.3.2. Description of clinical pathway of care

Several NHS policies address the importance of respiratory health, and focus on improving diagnosis and management of COPD, as well as reducing exacerbations. The NHS Long Term Plan includes better detection of COPD and increase of uptake in pulmonary rehabilitation, among others, as part of the respiratory priorities of the plan.(130) The NHS RightCare pathway for COPD provides a set of resources to support local health economies to address variation and improve health.(22) NICE's Clinical Knowledge summaries also sets goals with regards to managing breathlessness and preventing acute exacerbations of COPD.(131) Finally, aiming to address inequalities in care

provision, the NHSE CORE20Plus5 policy focuses on the most deprived 20% of the population which experience poorer than average health outcomes and focuses on five clinical areas, one of which is COPD.(23)

B.1.3.2.1. Care settings for the management of COPD

The setting of care for patients with COPD varies based on the severity of the disease, individual needs and available resources; however, COPD is most frequently managed in primary and community care. All of the possible settings of care are shown below.(33)

1. **Primary care (general practice):**
    - Most people with COPD initially seek care from their GP. GPs and the primary care team play a crucial role in diagnosing COPD, providing basic management and referring patients to specialised services when necessary.
    - While coverage is far from universal for the five fundamentals of care (Section B.1.3.2.2) GPs offer advice on lifestyle modifications, smoking cessation and vaccinations. GPs also prescribe inhaled medications (Table 16) and provide rescue packs comprising oral steroids and antibiotics. Primary (and community) care may also see people at the time of exacerbations, and support the use of rescue packs.
2. **Community-based services:**
    - Community respiratory teams provide support for COPD patients outside of hospitals. These teams include respiratory nurses, physiotherapists and other healthcare professionals.
    - They typically offer a combination of home visits, smoking cessation, pulmonary rehabilitation programmes and education on self-management, and oxygen services. Again, full access to all five fundamentals of care (Section B.1.3.2.2) is challenging in community settings (Section B.1.4).
3. **Hospital outpatient clinics:**
    - Respiratory outpatient clinics within hospitals provide specialised care for COPD patients. Patients attend these clinics for specific reasons, such as medication adjustments and assessments.
4. **Pulmonary rehabilitation centres:**
    - These trust-based centres offer structured programmes that combine exercise training, education and psychological support.
    - Pulmonary rehabilitation helps improve exercise capacity, reduce symptoms and enhance HRQoL for patients with COPD.
5. **Acute hospital care:**
    - For severe exacerbations or complications, COPD patients may require hospitalisation.
    - Acute care includes exacerbation management, support for respiratory failure and close monitoring. It also provides an opportunity to optimise maintenance therapies.

6. **Hospital at home schemes:**
    - Patients who have an exacerbation or worsening of their COPD can be safely cared for in 'hospital at home' schemes or discharged from hospital more quickly if they are rated as low risk on a clinical scoring system called DECAF.(132)

B.1.3.2.2. Treatment pathway for COPD in England

The goals of treatment of COPD are to reduce symptoms and the number and severity of exacerbations, improve exercise tolerance and health status, and reduce mortality.(3)

NICE has published diagnosis and management guidelines for people ≥16 years of age with COPD, which were last updated in July 2019.(7) The NICE guidelines recommend a combination of non-pharmacological and pharmacological treatment plans, which should be revised and adapted at regular time intervals based on the patient's response to treatment.(7)

A more recent international document is also available from GOLD, which was last updated in 2024.(3) GOLD does not refer to itself as a guideline, rather a strategy needing local implementation.

NICE 2019 guidelines

The NICE guidelines lay out five 'fundamentals of care' for patients with COPD which are both non-pharmacological and pharmacological in nature. These are:(7)

1. **Offer treatment and support to stop smoking**: Smoking cessation is crucial for managing COPD, as helping patients quit smoking can significantly improve their mortality, lung function and overall health.
2. **Provide pneumococcal and influenza vaccinations**: Vaccinations protect against respiratory infections, which can cause worsening of COPD symptoms including exacerbations. Pneumococcal and influenza vaccines are recommended for all patients with COPD.
3. **Offer pulmonary rehabilitation, if indicated**: Pulmonary rehabilitation programmes include exercise training, education and support. These practices help improve exercise capacity, reduce symptoms and enhance HRQoL for people with COPD.
4. **Co-develop a personalised self-management plan**: Collaborate with patients to create an individualised self-management plan. This plan should address symptom management, exacerbation prevention and coping strategies.
5. **Optimise treatment for comorbidities**: COPD often coexists with other health conditions. Managing comorbidities effectively is essential for overall wellbeing. Regularly review and adjust treatment plans based on individual needs.

Provision of these 'fundamentals' is not universal across England. For example, according to the NHS Long Term Plan published in January 2019, pulmonary rehabilitation was only offered to 13% of eligible patients, with a focus on those with more severe COPD.(130) The most recently published

survey from Asthma and Lung UK indicates that care for COPD patients has not returned to pre-pandemic levels and only 17.6% of individuals had received all five fundamentals.(39)

Pharmacological management

Inhaled therapies are recommended for patients who have been offered the appropriate non-pharmacological interventions but continue to experience breathlessness and exercise limitation, and/or exacerbations.(7) Before the initiation of inhaled therapies, patients should be trained and able to demonstrate competency in inhaler use technique.(7) Pharmacotherapy for COPD, inhaler technique and adherence should be reviewed and adapted regularly based on response.(7) Pharmacotherapy recommendations by the NICE 2019 guidelines for patients with COPD in England are outlined in Table 16.

Short-acting β2 and muscarinic antagonists (SABA and SAMA) are recommended as a first step to relieve breathlessness and exercise limitations.(7) For patients who continue to experience limiting symptoms and exacerbations, the NICE 2019 guidelines recommend inhaled treatment escalation to double therapy (LABA + LAMA or LABA + ICS) and then triple therapy (LABA + LAMA + ICS).(7)

The NICE 2019 guidelines recommend consideration of off-label add-on therapy with azithromycin for COPD non-smokers who continue to experience frequent (i.e., ≥4 per year) exacerbations, prolonged exacerbations with sputum production or exacerbations resulting in hospitalisation, despite optimised non-pharmacological and inhaled therapies, vaccinations and referral for pulmonary rehabilitation.(7) Roflumilast is recommended in NICE guidance (TA461) as add-on therapy for COPD patients with chronic bronchitis, FEV_1 <50% and ≥2 exacerbations in the last year, despite triple therapy.(133) There are currently no therapies recommended in England specifically for patients with COPD with Type 2 inflammation who continue to exacerbate despite triple therapy.

GOLD 2024 global strategy

The GOLD 2024 global strategy recommends similar non-pharmacological management of COPD as the NICE 2019 guidelines.(3)

The GOLD 2024 global strategy recommends add-on therapy with azithromycin for non-smokers or roflumilast for patients with FEV_1 <50% and chronic bronchitis, particularly for those with ≥1 serious exacerbation in the last year.(3) There are currently no therapies recommended by GOLD specifically for patients with COPD with Type 2 inflammation who continue to exacerbate despite triple therapy.

Pharmacological treatment recommendations by NICE 2019 and GOLD 2024 are outlined in Table 16.

Table 16. NICE 2019 and GOLD 2024 treatment guidelines for pharmacological management in COPD

	NICE 2019		GOLD 2024	
Initial therapy	• SABA or SAMA		• All patients should receive a SABA or SAMA for immediate symptom relief Group A: • A bronchodilator (short- or long-acting) Group B: • LABA + LAMA[a] Group E: • LABA + LAMA[a] • Consider LABA + LAMA + ICS[a] if blood EOS ≥300 cells/µL	
If patients continue to experience limiting symptoms (dyspnoea) or exacerbations on initial maintenance therapy				
	No asthmatic features/features suggesting steroid responsiveness[b]	**Asthmatic features/features suggesting steroid responsiveness[b]**	**Dyspnoea[c]**	**Exacerbations[c]**
Monotherapy	N/A	N/A	LABA or LAMA	LABA or LAMA
Double therapy	LABA + LAMA	LABA + ICS[d]	• LABA + LAMA[a] If no improvement: • Consider switching inhaler device or molecules • Implement or escalate non-pharmacological treatment(s) • Investigate (and treat) other causes of dyspnoea	If EOS <300 cells/µL: • LABA + LAMA[a] If EOS ≥300 cells/µL consider triple therapy directly
Triple therapy	Day-to-day symptoms that adversely impact QoL: • Consider 3-month trial of LABA + LAMA + ICS[d,e] • If no improvement, revert to LABA + LAMA One severe or 2 moderate exacerbations within a year: • Offer LABA + LAMA + ICS[d,e]	Day-to-day symptoms that adversely impact QoL, or 1 severe or 2 moderate exacerbations within a year: • Offer LABA + LAMA + ICS[d,e]	N/A	If further exacerbations on double therapy and EOS ≥100 cells/µL or single therapy and EOS ≥300 cells/µL: • Consider LABA + LAMA + ICS[a] • Consider de-escalation of ICS or switch if pneumonia, inappropriate original indication, or lack of response to ICS

	NICE 2019		GOLD 2024	
				If further exacerbations on double therapy and EOS <100 cells/µL consider add-on therapy directly
Add-on therapy	If chronic bronchitis, FEV_1 <50% and ≥2 exacerbation in the last year: • Roflumilast If non-smoker and continue to experience frequent (i.e., ≥4 per year) exacerbations despite optimised inhaled treatment (double or triple therapy): • Azithromycin (off-label)		If FEV_1 <50% and chronic bronchitis, particularly if ≥1 serious exacerbation in the last year: • Roflumilast If non-smoker: • Azithromycin (off-label)	

COPD = chronic obstructive pulmonary disease; EOS = eosinophils; FEV_1 = forced expiratory volume in 1 second; GOLD = Global Initiative for Chronic Obstructive Ling Disease; ICS = inhaled corticosteroids; LABA = long-acting β2 agonists; LAMA = long-acting muscarinic antagonists; N/A = not applicable; NICE = National Institute for Health Care Excellence; QoL = quality of life; SABA = short-acting β2 agonists; SAMA = short-acting muscarinic antagonists

[a] Single inhaler therapy may be more convenient and effective than multiple inhalers, as well as improving adherence to treatment.

[b] Asthmatic features/features suggesting steroid responsiveness in this context include any previous secure diagnosis of asthma or atopy, a higher blood EOS count, substantial (≥400 ml) variation in FEV_1 over time or substantial (≥20%) diurnal variation in peak expiratory flow.

[c] These treatment recommendations are not depended on the GOLD ABE assessment diagnosis.

[d] Be aware of an increased risk of side effects (including pneumonia) in people who take ICS.

[e] Document in clinical records the reason for continuing ICS treatment.

Source: NICE 2019 COPD guidelines(7) and GOLD 2024(3)

B.1.3.2.3. Current treatments for patients with uncontrolled COPD with Type 2 inflammation despite treatment with triple therapy

Recommended options beyond triple therapy for patients who continue to experience exacerbations include add-on treatment with roflumilast or azithromycin.(3, 7) However, both treatments have demonstrated limited efficacy and tolerability, particularly in patients with uncontrolled COPD and Type 2 inflammation (as measured by raised EOS).(3, 4, 7-12, 134-137) Market research conducted by Sanofi in the UK in 2023 has shown that clinicians perceive current treatment options beyond triple therapy to be very limited.(33)

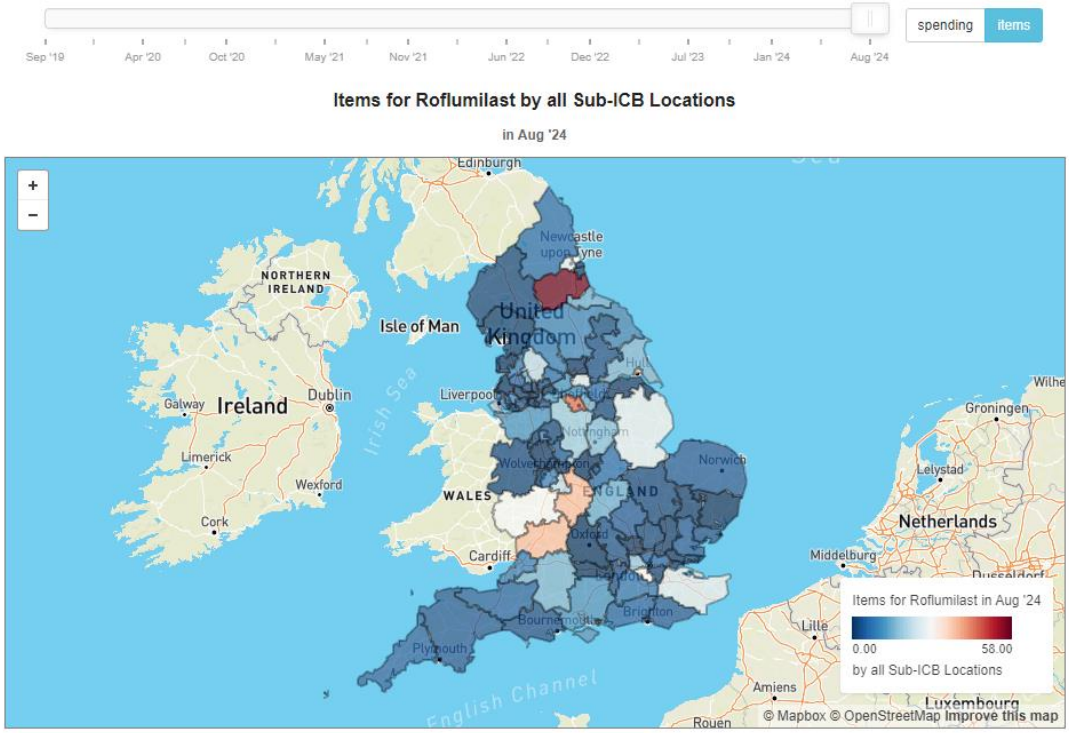
Roflumilast

Roflumilast, a phosphodiesterase-type-4 (PDE4) inhibitor, is indicated as maintenance treatment for severe COPD (FEV_1 <50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add-on to bronchodilator treatment.(138) NICE guidance (TA461) limits the use of roflumilast to patients with severe COPD (FEV_1 <50% predicted) and two or more exacerbations in the past year despite triple therapy.(133) In contrast, dupilumab is indicated for adults with uncontrolled COPD (≥2 moderate or ≥1 severe historical exacerbations within 12 months) characterised by raised blood EOS (≥300 cells/μL) on triple therapy (or double therapy when ICS is not appropriate).(1, 2) Roflumilast is contraindicated for patients with moderate-severe hepatic impairment, and is not recommended for patients with congestive heart failure or a history of depression associated with suicidal ideation or behaviour, and should be carefully assessed for patients with existing psychiatric symptoms.(138) The overlap between the roflumilast and dupilumab target populations is therefore limited, and roflumilast treatment is limited by specific patient contraindications and precautions.

Despite the availability of the NICE recommendation for roflumilast (TA461) since 2017,(133) very few patients have been initiated on roflumilast in clinical practice in England. To understand the uptake of roflumilast in England, we analysed GP prescribing data for the 250 mg presentation of roflumilast,(139) which is used for the first month of treatment.(138) Based on GP prescribing data for 2020 to 2023, an average of 909 patients per year initiated roflumilast.(139) To estimate the total number of patients that are eligible for roflumilast based on the criteria set out in TA461 (FEV_1 <50% [i.e., grade 3 or 4] and ≥2 exacerbations in the past 12 months despite triple inhaled therapy),(133) we used data from an electronic health records study of 340,515 COPD patients in England, which reported that 8.3% (20,993/251,714) of patients had FEV_1 <50% and ≥2 exacerbations, and 18% (59,980/340,515) of patients in the study received triple therapy.(26) Based on 2022/2023 QOF data on the total number of patients with COPD in England (1,151,474),(56) this results in an estimated 16,916 patients who should be eligible for roflumilast. In reality, only 909 of these 16,916 patients (5.4%) actually received roflumilast.

Prescribing data (Figure 10), as well as clinicians we have spoken to, indicate that the vast majority of centres have only single figures of patients on roflumilast, with some clinicians not having any patients on roflumilast for over 10 years.

Figure 10. Prescribing data for roflumilast in England (August 2024)



For clarity, practice graphs and maps only show standard GP practices, and exclude non-standard settings like prisons, out-of-hours services, etc. CCG boundaries from NHS England. Practice locations are approximate, based on postcode. Only practices with a known location are shown here. PCN boundaries are illustrative only.

Source: Open Prescribing 2024(139)

The low initiation rate of roflumilast in England reflects a number of limitations of the treatment, particularly with regards to its efficacy and tolerability.

In the pivotal REACT and RE2SPOND trials, roflumilast showed a reduction in the rate of moderate or severe exacerbations compared with placebo in patients with blood EOS ≥300 cells/μL (rate ratio: 0.77; 95% CI: 0.61, 0.97; p=0.0264), but failed to demonstrate a statistically significant reduction in severe exacerbations in this subgroup (rate ratio: 0.81; 95% CI: 0.52, 1.25; p=0.3379).(140) Additionally, in the ITT populations, roflumilast had no impact on HRQoL or symptoms (as assessed by CAT score) compared to placebo.(136, 137)

Roflumilast is associated with a high incidence of adverse events (AEs) in both clinical trials and real-world studies. The most common AEs reported with roflumilast are diarrhoea, nausea, weight loss, insomnia and depressive mood symptoms.(134, 138, 141-145) In clinical trials and real-world practice, these AEs, particularly the gastrointestinal effects, have led to high discontinuation rates of approximately 30% and 70%, respectively.(136, 137, 144, 146) In England, roflumilast is not recommended for use in patients with severe immunological diseases, severe acute infectious diseases, cancer, congestive heart failure or patients with a history of depression associated with suicidal ideation or behaviour.(138) Additionally, in 2014, the MHRA published a drug safety update warning on the risk of suicidal behaviour associated with the use of roflumilast.(147)

In real-world studies, the potential benefits of roflumilast as add-on to triple therapy are limited to a minority of patients due to the substantial proportion of patients who discontinue treatment (up to 70%).(142, 144-146) In patients with early discontinuation, roflumilast did not demonstrate any reduction in exacerbation rates in real-world practice.(145)

According to clinicians we have spoken with, the generally low initiation of roflumilast in England is due to a perception of low efficacy and tolerability, derived from the clinical trial results, real-world evidence and their own first-hand experiences with roflumilast. Clinicians report weight loss as a particular concern given that patients with COPD who are underweight or have a low BMI have a poorer prognosis.(148) Low tolerability also results in high discontinuation rates in those patients who are initiated. Clinicians have stated that most patients discontinue roflumilast treatment within six months. Specifically, 50% stop due to gastrointestinal side effects within the first two months, 25% stop within six months due to lack of efficacy, and another 25% stop within six months due to a lack of perceived benefit and side effects.

As described above, roflumilast discontinuation rates are high in clinical trials, and even higher in real world evidence studies. To gain insights into treatment duration with roflumilast in real world practice in England, we analysed prescription data for roflumilast by presentation. Roflumilast is available in two presentations, 250 mg and 500 mg. The 250 mg tablets are used once daily for the first month as the starting dose, followed by 500 mg daily, subject to tolerability.(138) Data from Open Prescribing for the years 2020 to 2023 for the two presentations are shown in Table 17.(139) The table indicates an average ratio of 7 between the 250 mg starting dose and the 500 mg maintenance dose, indicating that on average patients typically remain on roflumilast for approximately 8 (1+7) months, which is higher but generally in line with the clinicians' estimates. Such a short average treatment duration in the real world raises questions regarding the long-term efficacy that can be achieved with roflumilast, and whether roflumilast represents a viable "maintenance" treatment.

Table 17. Total packs of roflumilast 250 mg and 500 mg

Year	Roflumilast 250 mg	Roflumilast 500 mg	500:200 mg ratio
2020	677	5,792	8.6
2021	860	6,256	7.3
2022	973	6,958	7.2
2023	1,124	7,356	6.5
Total	**3,634**	**26,362**	**7.3**

Source: Open Prescribing 2024(139)

Azithromycin

Azithromycin, a macrolide antibiotic, is not approved for the treatment of patients with COPD in England.(6) However, the NICE 2019 guidelines recommend off-label use of azithromycin prophylactically only for patients who are non-smokers and continue to experience frequent (i.e., ≥4 per year) exacerbations despite optimised inhaled treatment (double or triple therapy).(7, 149) Azithromycin should not be prescribed in patients with severe hepatic impairment, and with caution in patients with mild-moderate hepatic impairment, QT prolongation, bradycardia, cardiac arrhythmia or severe cardiac insufficiency, electrolyte disturbances and

severe renal impairment, or myasthenia gravis.(150) There is limited overlap between this population and the dupilumab label population and azithromycin treatment is limited by specific patient precautions.

Azithromycin places a further time and resource burden on the NHS as it mandates additional testing prior to prescription (including sputum culture and sensitivity to exclude non-tuberculous mycobacteria, thoracic CT, electrocardiography for risk of corrected QT interval [QTc] prolongation and baseline liver function testing), as well as ongoing monitoring to assess the risk/benefit ratio.(7, 149)

As an antibiotic, azithromycin inhibits bacterial protein synthesis.(151) Bacterial infection is associated with approximately 50% of acute exacerbations of COPD,(152) and therefore prophylactic azithromycin may reduce the risk of bacterial infection and associated neutrophilic airway inflammation, reducing exacerbation risk.(153) Even though the specific mechanism of action for azithromycin remains unclear, it does not target the underlying pathophysiology of COPD.(151) Additionally, long-term treatment with macrolides has been shown to significantly increase the Type 2 inflammatory mediators (e.g., IL-4, and IL-13) that are targeted by dupilumab.(154)

Azithromycin lacks specific clinical evidence in patients with uncontrolled COPD (≥2 moderate or ≥1 severe historical exacerbations within 12 months) and Type 2 inflammation (blood EOS ≥300 cells/μL; the target population for dupilumab). Additionally, azithromycin has very limited evidence to support its use as add-on to triple therapy. The efficacy of azithromycin as add-on to triple therapy has only been assessed in post-hoc subgroup analyses, with statistically significant reductions in moderate exacerbations but no available evidence on FEV_1 or HRQoL improvement.(4, 5) Overall, there is no clear population or subpopulation identified in which azithromycin provides added benefit.

Use of azithromycin carries the risk of hearing loss and prolongation of the QTc, and is also associated with a substantial increase in the development of antimicrobial resistance (AMR) in the individual and populations.(3, 4, 7-12) A meta-analysis of clinical trials in patients with chronic lung diseases demonstrated that treatment with azithromycin significantly increased the incidence of AMR by 170% vs. placebo.(155) In patients with COPD specifically, AMR was increased by 270% with azithromycin vs. placebo.(155) Another study found an increase in resistant bacteria in 81% of COPD patients treated with azithromycin, versus 41% with placebo.(4) A study of long-term azithromycin usage has suggested that development of AMR may result in waning of efficacy over time.(156) Supporting this, a study in patients with stable COPD demonstrated that an approximately 6-fold higher concentration of azithromycin is required to achieve microbicidal effect post-treatment compared with the concentration required pre-treatment.(12) The specific cost of AMR due to azithromycin in the UK is not readily available. However, the overall economic burden of AMR in the UK is substantial, adding over £1 billion annually to healthcare and societal costs.(157)

Macrolide resistance is rapidly inducible, highly transferrable and increasing in prevalence in line with increasing macrolide prescriptions.(158) The significant risks associated with increasing AMR through continued inappropriate antibiotic prescribing practices (including those for azithromycin in COPD) are addressed in multiple national and international programmes that promote antimicrobial stewardship (Section B.3.2.4.3). This

includes NICE, who offer guidelines (NG15) and a quality standard (QS121) to promote "antimicrobial stewardship" in England.(159, 160)

B.1.3.2.4. Unmet need

COPD is a debilitating and progressive disease associated with a high clinical (Section B.1.3.1.3), humanistic (Section B.1.3.1.4) and economic burden (Section B.1.3.1.5), driven by airflow obstruction severity, symptom burden, and the frequency and severity of exacerbations. Despite treatment with triple inhaled therapy, almost two-thirds of patients with COPD continue to experience moderate to severe exacerbations:(26, 40)

- Post-hoc analyses of the IMPACT trial showed that, regardless of exacerbation history, 45% to 51% of patients on triple therapy continued to experience moderate or severe exacerbations.(40)
- In a UK observational database study of patients with COPD aged ≥40 years who were receiving triple therapy at baseline (n=59,980), 62% had at least one moderate or severe exacerbation at baseline.(26)

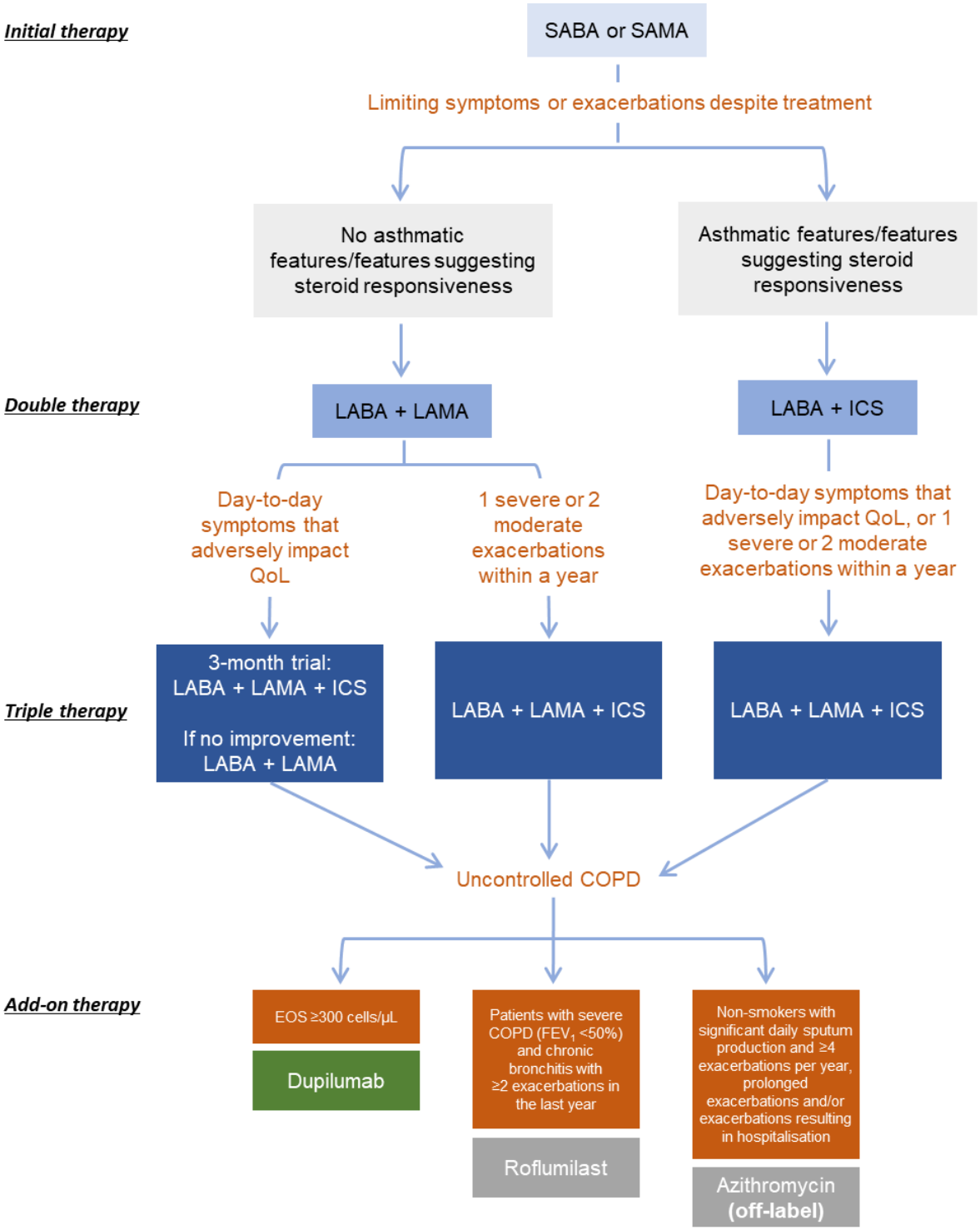
The risk of experiencing moderate or severe exacerbations is even greater in patients with COPD and Type 2 inflammation (raised blood eosinophils).(42) Among patients with COPD who experienced ≥1 severe or ≥2 moderate exacerbations despite triple therapy in a UK-based observational study (n=6,480), 37.2% had blood EOS counts ≥250 cells/μL and 20.3% had blood EOS counts ≥350 cells/μL.(161)

Currently available treatments for patients who continue to experience exacerbations despite triple therapy (or double therapy if ICS is not appropriate) are non-targeted. Roflumilast, which is only indicated for maintenance treatment of severe COPD (FEV_1 <50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add-on to bronchodilator treatment,(138) is associated with numerous gastrointestinal side effects as well as insomnia, depressive mood symptoms and risk of suicidal behaviour, with discontinuation rates reported to be as high as 67% in real-world practice.(136, 137, 142, 144, 145) Azithromycin is not licenced for use in COPD and carries the risk of severe AEs as well as high rates of antibiotic resistance.(4, 8)

There is an unmet need for a targeted, effective and well-tolerated treatment that can provide significant clinical improvements in exacerbations, lung function, HRQoL and symptoms in patients with uncontrolled COPD. The unmet need is arguably greater for those patients with Type 2 inflammation (raised blood EOS), who experience a higher burden and worse prognosis than those without Type 2 inflammation. Dupilumab specifically targets Type 2 inflammation (blood EOS ≥300 cells/μL) and has demonstrated significant benefits broadly across clinically relevant outcomes in patients who uncontrolled COPD (≥2 moderate or ≥1 severe historical exacerbations within 12 months) despite triple therapy (Section B.2).

The proposed positioning of dupilumab in the treatment pathway for COPD in England is depicted in Figure 11. It is anticipated that dupilumab will be used according to licence, as add-on maintenance treatment for uncontrolled COPD (≥1 severe exacerbation or ≥2 moderate exacerbations) characterised by raised blood EOS (≥300 cells/μL; Type 2 inflammation) on triple therapy (or double therapy if ICS is not appropriate).(1, 2)

Figure 11. Clinical pathway of care for COPD in England including the proposed positioning of dupilumab



"Asthmatic features/features suggesting steroid responsiveness" include previous diagnosis of asthma or atopy, a higher blood EOS count, substantial variation in FEV_1 over time (≥400 mL) or substantial diurnal variation in peak expiratory flow (≥20%).(7)
COPD = chronic obstructive pulmonary disease; EOS = eosinophils; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; LABA = long-acting β2 agonists; LAMA = long-acting muscarinic antagonists; QoL = quality of life; SABA = short-acting β2 agonists; SAMA = short-acting muscarinic antagonists
Source: Adapted from NICE 2019 COPD guidelines(7)

B.1.4. Equality considerations

COPD is a debilitating disease that disproportionately affects people of certain demographics.(162, 163) Based on data for 2022/23 published by Public Health England, people from the poorest 10% of households (Index of Multiple Deprivation Decile 1) were 1.7 times more likely to develop COPD than people from the most affluent 10% of households (Index of Multiple Deprivation Decile 10).(163) Higher levels of social deprivation have also been associated with an increased risk of exacerbations among patients with COPD in the UK.(88) In England between March 2021 and January 2023, age-standardised mortality rates due to COPD were highest in the most deprived areas, among people who had never worked or were in long term unemployment, and men of Bangladeshi background.(162) Age-standardised mortality rates due to COPD were consistently higher in men than in women across all regions in England.(162)

There is wide regional variation in outcomes for patients with COPD. For example, the latest atlas of health variation for respiratory disease (with data from 2015 to 2017 split by clinical commissioning group [CCG]) shows that the mortality rate from COPD ranged from 27.4 to 108.8 per 100,000 population, which is a 4.0-fold difference between geographical areas (CCGs) with the worst outcomes in the North and Northeast of England.(17) Note the English average mortality rate for 2015 to 2017 was 52.7 per 100,000 population.(17)

Disparities in care for patients with COPD have also been noted in England. In a 2011 audit of chronic disease management in London, Black patients were less likely to be prescribed pharmacological treatments including SABAs, SAMAs, LAMAs and ICS + LABA than patients of White background, while patients with South Asian heritage were less likely to receive LAMAs than White patients.(164) Black and South Asian patients were also less likely to be referred for COPD pulmonary rehabilitation than patients of White background.(164) Further, despite advice that oral corticosteroids (OCS) use should be minimised due to the risks associated with long term use,(7) a study conducted by Sanofi in collaboration with the York Health Economics Consortium found that prescribing of OCS was nearly 50% higher in patients with COPD or asthma from the most deprived areas than in those from the least deprived areas.(165) There is also significant geographic variation in access to pulmonary rehabilitation across England, with substantially lower provision in the North West than the South East.(166) Among patients with COPD surveyed by Asthma + Lung UK in 2023 (N=2,748), less than half of eligible respondents (48%) had received pulmonary rehabilitation; 70% of these patients had not been offered pulmonary rehabilitation despite being eligible.(166)

This submission does not discriminate against any of these patient groups; however, it is worth noting that the current lack of licenced, reimbursed, effective treatments with a favourable safety profile in this indication already places these patients at a significant disadvantage compared to patients with other chronic diseases (e.g., rheumatology, CVD, diabetes) who have had access to advanced treatments for several years. Therefore, a NICE recommendation in this indication could have a positive impact on people protected by the equality legislation.

Clinical experts in England consulted by Sanofi as part of an advisory board meeting in July 2024 confirmed that there are known inequalities in COPD care in the UK, and noted that introduction of dupilumab has the

potential to alleviate inequalities in COPD as patients will have equal access to dupilumab across all regions of the UK (in contrast to pulmonary rehabilitation) and dupilumab will be the first advanced therapy for COPD (reducing inequalities compared to other chronic diseases have had access to advanced treatments for several years).(167)

B.2. Clinical effectiveness

A systematic literature review (SLR) identified two high-quality clinical trials for dupilumab in the relevant patient population as defined by the NICE scope (i.e., BOREAS and NOTUS)

- BOREAS and NOTUS are replicate phase 3, placebo-controlled double-blind, randomised, multicentre international trials, investigating dupilumab vs. placebo as add-on maintenance treatment for COPD patients with Type 2 inflammation (blood EOS ≥300 cells/μL), who are uncontrolled (≥2 moderate or ≥1 severe historical exacerbations within 12 months) on triple therapy (LABA + LAMA + ICS).
- The primary endpoint was the annualised rate of moderate or severe COPD exacerbations over the 52-week treatment period.
- The individual and pooled analysis results from both trials are presented in this submission and have informed the economic analysis.

BOREAS and NOTUS have robustly demonstrated the efficacy of dupilumab in uncontrolled COPD with Type 2 inflammation.

- Dupilumab resulted in a significant and clinically meaningful reduction of 31% in the annualised rate of moderate or severe exacerbations compared to placebo. These results were consistent across the 52 week treatment period.
- Dupilumab resulted in a significant and clinically meaningful increase of 83 mL in pre-BD FEV_1 at Week 12, compared to placebo. These results were maintained across the 52 week treatment period.
- Quality of life, as measured by SGRQ, was significantly better with dupilumab treatment compared to placebo.
- COPD symptoms, as measured by E-RS: COPD, were significantly improved with dupilumab treatment compared to placebo.

The safety profile of dupilumab is acceptable and consistent with existing safety data in patients with atopic dermatitis, asthma and chronic rhinosinusitis with nasal polyps (CRSwNP)

- In the BOREAS and NOTUS trials, dupilumab demonstrated a favourable benefit-risk and tolerability profile in COPD.
- Dupilumab has an established robust safety profile, validated by clinical trials and further supported by real-world safety data across multiple indications, with no new safety signals identified in patients with COPD.

The consistency of outcome results between the two trials, and in the combined analysis, are confirmatory of the efficacy observed. Additionally, positive outcomes across multiple domains; exacerbation risk, lung function, symptoms and quality of life, are indicative of a treatment that effectively targets the underlying drivers of disease in these patients (Type 2 inflammation).

Dupilumab has the potential to generate a significant step-change in the effective treatment of uncontrolled COPD with Type 2 inflammation, providing meaningful benefits to a burdened patient population with limited treatment options.

B.2.1. Identification and selection of relevant studies

A systematic literature review (SLR) was conducted with a cut-off date of August 2024, to identify studies reporting on the clinical efficacy and safety of dupilumab and its comparators in adults with COPD and raised blood EOS (≥300 cells/µL) who are uncontrolled on triple therapy (long-acting β_2-agonist [LABA] + long-acting muscarinic antagonist [LAMA] + ICS) or double therapy (LABA + LAMA) if ICS is not appropriate (Appendix D.1).

A total of 3,136 publications were identified in the database searches and following removal of duplicates, 2,542 publications underwent title and abstract screening. Overall, 210 publications were selected for full-text screening and 13 publications were included in the SLR. These 13 publications reported data from four primary RCTs, three post-hoc analyses of RCTs and five post-hoc pooled analyses of RCTs. Among the RCTs identified, two investigated dupilumab (BOREAS and NOTUS) and are described in detail below.

B.2.2. List of relevant clinical effectiveness evidence

Two replicate phase 3 RCTs, BOREAS (NCT03930732) and NOTUS (NCT04456673), support the use of dupilumab as add-on maintenance treatment for adults with uncontrolled COPD (≥2 moderate or ≥1 severe historical exacerbations within 12 months) and Type 2 inflammation (blood EOS ≥300 cells/µL) on triple therapy (LABA + LAMA + ICS) or double therapy (LABA + LAMA) if ICS is not appropriate (168, 169) A summary of the BOREAS and NOTUS trials is provided in Table 18.

Table 18. Clinical effectiveness evidence

Study	BOREAS (NCT03930732)	NOTUS (NCT04456673)
Study design	Phase 3, placebo-controlled, double-blind, randomised multicentre, international trial	Phase 3, placebo-controlled, double-blind, randomised multicentre, international trial
Population	Participants aged 40 to 80 years with moderate-to-severe COPD with evidence of Type 2 inflammation (blood EOS ≥300 cells/µL) who are uncontrolled (≥2 moderate or ≥1 severe historical exacerbations within 12 months) on LABA + LAMA + ICS (or LABA + LAMA if ICS is not appropriate)	Participants aged 40 to 85 years with moderate-to-severe COPD with evidence of Type 2 inflammation (blood EOS ≥300 cells/µL) who are uncontrolled (≥2 moderate or ≥1 severe historical exacerbations within 12 months) on LABA + LAMA + ICS (or LABA + LAMA if ICS is not appropriate)
Intervention(s)	Dupilumab SC 300 mg q2w + background therapy (triple therapy or double therapy if ICS is not appropriate)	Dupilumab SC 300 mg q2w + background therapy (triple therapy or double therapy if ICS is not appropriate)
Comparator(s)	Placebo q2w + background therapy (triple therapy or double therapy if ICS is not appropriate)	Placebo q2w+ background therapy (triple therapy or double therapy if ICS is not appropriate)
Indicate if study supports application for marketing authorisation	Yes	Yes

Study	BOREAS (NCT03930732)	NOTUS (NCT04456673)
Indicate if study used in the economic model	Yes	Yes
Rationale if study not used in model	N/A	N/A
Reported outcomes specified in the decision problem	Primary efficacy endpoint: • **Annualised rate of moderate or severe COPD exacerbations over the 52-week treatment period[a]** Key secondary efficacy endpoints: • **Change from baseline to Week 12 and Week 52 in pre-BD FEV_1** • **Change from baseline to Week 52 in SGRQ total score[b]** • Proportion of participants with an improvement in SGRQ score of ≥4 points (MCID) from baseline to Week 52 Other secondary efficacy endpoints: • **Change from baseline to Weeks 2, 4, 8, 24, 36 and 44 in pre-BD FEV_1** • Change from baseline to Weeks 2, 4, 8, 12, 24, 36 and 52 in post-BD FEV_1 • Change from baseline to Weeks 2, 4, 8, 12, 24, 36, 44 and 52 in FEF 25-75% • **Annualised rate of severe COPD exacerbations over the 52-week treatment period** • Time to first moderate or severe COPD exacerbation during the 52-week treatment period Tertiary/exploratory efficacy endpoints: • Annualised loss of lung function as assessed by a FEV_1 slope analysis • Change from baseline to Weeks 12, 24 and 52 in FVC • Evaluation of clinical COPD respiratory symptoms using E-RS: COPD in the EXACT tool[c] • Annualised rate of COPD exacerbations assessed by the EXACT tool over 52 weeks • Time to first severe COPD exacerbation during the 52-week treatment period	Primary efficacy endpoint: • **Annualised rate of moderate or severe COPD exacerbations over the 52-week treatment period[a]** Key secondary efficacy endpoints: • **Change from baseline to Week 12 and Week 52 in pre-BD FEV_1** • **Change from baseline to Week 52 in SGRQ total score[b]** • Proportion of participants with an improvement in SGRQ score of ≥4 points (MCID) from baseline to Week 52 Other secondary efficacy endpoints: • **Change from baseline to Weeks 2, 4, 8, 24, 36 and 44 in pre-BD FEV_1** • Change from baseline to Weeks 2, 4, 8, 12, 24, 36 and 52 in post-BD FEV_1 • Change from baseline to Weeks 2, 4, 8, 12, 24, 36, 44 and 52 in FEF 25-75% • **Annualised rate of severe COPD exacerbations over the 52-week treatment period** • Time to first moderate or severe COPD exacerbation during the 52-week treatment period Tertiary/exploratory efficacy endpoints: • Annualised loss of lung function as assessed by a FEV_1 slope analysis • Change from baseline to Weeks 12, 24 and 52 in FVC • Evaluation of clinical COPD respiratory symptoms using E-RS: COPD in the EXACT tool[c] • Annualised rate of COPD exacerbations assessed by the EXACT tool over 52 weeks • Time to first severe COPD exacerbation during the 52-week treatment period • **Change from baseline in EQ-5D-5L single index score** and EQ VAS score **at Week 24 and Week 52**

Study	BOREAS (NCT03930732)	NOTUS (NCT04456673)
	Safety endpoints: • **AEs/TEAEs** • Potentially clinically significant laboratory abnormalities in haematology, biochemistry and urinalysis • ADA against dupilumab	Safety endpoints: • **AEs/TEAEs** • Potentially clinically significant laboratory abnormalities in haematology, biochemistry and urinalysis • ADA against dupilumab
All other reported outcomes	Tertiary/exploratory efficacy endpoints: • Increase in number of controller medication after exacerbation • Increase in patient total daily dose of controller medication after exacerbation	Tertiary/exploratory efficacy endpoints: • Increase in number of controller medication after exacerbation • Increase in patient total daily dose of controller medication after exacerbation

[a] Moderate exacerbations defined as exacerbations requiring systemic glucocorticoid treatment and/or antibiotic treatment. Severe exacerbations defined as those requiring hospitalisation or emergency department visit, or resulting in death. For both moderate and severe exacerbations to be counted as separate events, they must have occurred ≥14 days apart.
[b] Score range: better (0) to worse (100) quality of life; MCID = 4 points.
[c] Score range: less (0) to more (40) severe respiratory symptoms.
ADA = anti-drug antibody; AE = adverse event; BD = bronchodilator; COPD = chronic obstructive pulmonary disease; EOS = eosinophils; E-RS: COPD = Evaluating Respiratory Symptoms in COPD; EXACT = Exacerbations of Chronic Pulmonary Disease Tool; FEF = forced expiratory flow; FEV_1 = forced expiratory volume in 1 second; FVC = force vital capacity; ICS = inhaled corticosteroids; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; MCID = minimum clinically important difference; N/A = not applicable; q2w = every two weeks; SC = subcutaneous; SGRQ = St. George's Respiratory Questionnaire; TEAE = treatment emergent adverse event
Source: Bhatt et al. 2023(168); Bhatt et al. 2024(169)

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1. Study methodology

A summary of the study designs and methodology of the BOREAS (NCT03930732) and NOTUS (NCT04456673) trials is presented in Table 19. Note, EQ-5D-5L data were only collected at baseline in BOREAS, while in NOTUS, EQ-5D data were collected at baseline, Week 24 and Week 52.(168, 169)

Table 19. Comparative summary of trial methodology

Trial number (acronym)	BOREAS (NCT03930732)	NOTUS (NCT04456673)
Location	Argentina, Bulgaria, Canada, Chile, China, Czech Republic, Denmark, Finland, Germany, Hungary, Israel, Italy, Japan, Republic of Korea, Mexico, Poland, Romania, Russian Federation, Slovakia, Spain, Sweden, Turkey, Ukraine, United States	Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Czech Republic, France, Germany, Greece, Hungary, Latvia, Lithuania, Mexico, Netherlands, Peru, Poland, Portugal, Romania, Russian Federation, Serbia, Slovakia, South Africa, Spain, Ukraine, United Kingdom, United States
Trial design	Phase 3, placebo-controlled, double-blind, randomised multicentre, international trial	Phase 3, placebo-controlled, double-blind, randomised multicentre, international trial
Eligibility criteria for participants	**Key inclusion criteria:** • Patients aged ≥40 to ≤80 years at the time of signing the informed consent • Physician diagnosis of COPD • Current or former smokers with a smoking history of ≥10 pack-years • Moderate-to-severe COPD (post-BD FEV_1/FVC ≤0.7 and post-bronchodilator FEV_1 % predicted >30% and ≤70%) • MRC dyspnoea score of grade ≥2[a] • Patient-reported history of signs and symptoms of chronic bronchitis (chronic productive cough) for 3 months in the year up to screening in the absence of other known causes of chronic cough • Documented history of high exacerbation risk defined as exacerbation history of ≥2 moderate[b] or ≥1 severe[c] within the year prior to inclusion o ≥1 exacerbation occurring while on treatment with LABA + LAMA + ICS (or LABA + LAMA, if ICS was not appropriate	**Key inclusion criteria:** • Patients aged ≥40 to ≤85 years at the time of signing the informed consent • Physician diagnosis of COPD • Current or former smokers with a smoking history of ≥10 pack-years • Moderate-to-severe COPD (post-BD FEV_1/FVC ≤0.7 and post-bronchodilator FEV_1 % predicted >30% and ≤70%) • MRC dyspnoea score of grade ≥2[a] • Patient-reported history of signs and symptoms of chronic bronchitis (chronic productive cough) for 3 months in the year up to screening in the absence of other known causes of chronic cough • Documented history of high exacerbation risk defined as exacerbation history of ≥2 moderate[b] or ≥1 severe[c] within the year prior to inclusion o ≥1 exacerbation occurring while on treatment with LABA + LAMA + ICS (or LABA + LAMA, if ICS was not appropriate)

Trial number (acronym)	BOREAS (NCT03930732)	NOTUS (NCT04456673)
	○ One of the two required moderate exacerbations has to require the use of systemic corticosteroids • Background triple therapy (LABA + LAMA + ICS) for 3 months prior to randomisation with a stable dose of medication for ≥1 month prior to Visit 1. Double therapy (LABA + LAMA) allowed if ICS not appropriate • Blood EOS ≥300 cells/μL (evidence of Type 2 inflammation) at screening **Key exclusion criteria:** • COPD diagnosis for <12 months prior to randomisation • Current or prior asthma diagnosis • Significant non-COPD pulmonary diseases or another diagnosed pulmonary or systemic disease associated with elevated peripheral EOS counts • Cor pulmonale or signs of right-sided heart failure • Treatment with oxygen of more than 12 hours per day • Hypercapnia with bi-level ventilation • Acute COPD exacerbation or respiratory tract infection ≤4 weeks prior to or during screening • History of, or planned pneumonectomy or lung volume reduction surgery • Initiation of a pulmonary rehabilitation programme ≤4 weeks before screening • Diagnosis of α-1 anti-trypsin deficiency • History of clinically significant renal, hepatic, cardiovascular, metabolic, neurologic, haematologic, ophthalmologic, respiratory, gastrointestinal, cerebrovascular, substance and/or alcohol abuse, prior history of malignancy or active malignancy within 5 years prior to baseline, or other significant medical illness or disorder which, in the judgement of the investigator, could interfere with the study or require treatment that might interfere with the study • Patients with active autoimmune disease or patients using immunosuppressive therapy for autoimmune disease	○ One of the two required moderate exacerbations has to require the use of systemic corticosteroids • Background triple therapy (LABA + LAMA + ICS) for 3 months prior to randomisation with a stable dose of medication for ≥1 month prior to Visit 1. Double therapy (LABA + LAMA) allowed if ICS not appropriate • Blood EOS ≥300 cells/μL (evidence of Type 2 inflammation) at screening **Key exclusion criteria:** • COPD diagnosis for <12 months prior to randomisation • Current or prior asthma diagnosis • Significant non-COPD pulmonary diseases or another diagnosed pulmonary or systemic disease associated with elevated peripheral EOS counts • Cor pulmonale or signs of right-sided heart failure • Long-term treatment with oxygen >4.0 L/min *or* >2.0 L/min required in order to maintain oxygen saturation >88% • Hypercapnia with bi-level ventilation • Acute COPD exacerbation or respiratory tract infection ≤4 weeks prior to or during screening • History of, or planned pneumonectomy or lung volume reduction surgery • Initiation of a pulmonary rehabilitation programme ≤4 weeks before screening • Diagnosis of α-1 anti-trypsin deficiency • History of clinically significant renal, hepatic, cardiovascular, metabolic, neurologic, haematologic, ophthalmologic, respiratory (apart from COPD), gastrointestinal, cerebrovascular, substance and/or alcohol abuse, prior history of malignancy or active malignancy within 5 years prior to baseline, or other significant medical illness or disorder which, in the judgement of the investigator, could interfere with the study or require treatment that might interfere with the study • Patients with active autoimmune disease or are using immunosuppressive therapy for an autoimmune disease

Trial number (acronym)	BOREAS (NCT03930732)	NOTUS (NCT04456673)
Settings and locations where the data were collected	275 sites in 24 countries	329 sites in 29 countries
Trial drugs	Participants were randomised (1:1) to receive either: • Dupilumab SC 300 mg q2w (n=468) • Matching placebo q2w (n=471) Administered for 52 weeks as add-on to background therapy (LABA + LAMA + ICS, or LABA + LAMA if ICS is not appropriate)	Participants were randomised (1:1) to receive either: • Dupilumab SC 300 mg q2w (n=470) • Matching placebo q2w (n=465) Administered for 52 weeks as add-on to background therapy (LABA + LAMA + ICS, or LABA + LAMA if ICS is not appropriate)
Permitted and disallowed concomitant medication	**Permitted:** • Maintenance treatment at a stable dose with LABA + LAMA + ICS • Systemic corticosteroids in the event of acute exacerbation for ≤6 weeks • Rescue medication with SABA and/or short-acting antimuscarinics (e.g., atrovent) **Prohibited:** • Any biologic agent within 5 half-lives (6 months if half-life unknown) of study entry and throughout study • PDE-4 inhibitors or theophylline unless stable >6 months before screening • New chronic macrolide antibiotic use (except during exacerbation for ≤28 days) • Systemic immunosuppressants • Intravenous immunoglobin therapy • Live attenuated vaccines • Beta-adrenergic receptor blockers (except for a selective beta-1 adrenergic receptor blocker used with dose stable 1 month prior to Visit 1) • Other clinical trial medication	**Permitted:** • Maintenance treatment at a stable dose with LABA + LAMA + ICS • Systemic corticosteroids in the event of acute exacerbation for ≤6 weeks • Rescue medication with SABA or short-acting antimuscarinics (e.g., atrovent) **Prohibited:** • Any biologic agent within 5 half-lives (6 months if half-life unknown) of study entry and throughout study • PDE-4 inhibitors or theophylline unless stable >6 months before screening • New chronic macrolide antibiotic use (except during exacerbation for ≤28 days) • Systemic immunosuppressants • Intravenous immunoglobin therapy • Live attenuated vaccines • Beta-adrenergic receptor blockers (except for a selective beta-1 adrenergic receptor blocker used with dose stable 1 month prior to Visit 1) • Other clinical trial medication

Trial number (acronym)	BOREAS (NCT03930732)	NOTUS (NCT04456673)
Primary outcomes (including scoring methods and timings of assessments)	Annualised rate of moderate[b] or severe[c] COPD exacerbations over the 52-week treatment period, defined as the number of exacerbation events (moderate or severe) from randomisation through Week 52 per patient-year	Annualised rate of moderate[b] or severe[c] COPD exacerbations over the 52-week treatment period, defined as the number of exacerbation events (moderate or severe) from randomisation through Week 52 per patient-year
Other outcomes used in the economic model/specified in the scope	**Lung function** • Change from baseline in pre-BD FEV_1, post-BD FEV_1, FEF 25-75% and FVC • Annualised loss of lung function as assessed by a FEV_1 slope analysis • **FEV_1% predicted by GOLD stage at Week 52** *(post-hoc analysis)* **Incidence and severity of acute exacerbations** • Annualised rate of severe COPD exacerbations over the 52-week treatment period • Time to first moderate or severe COPD exacerbation during the 52-week treatment period • Time to first severe COPD exacerbation during the 52-week treatment period • Annualised rate of COPD exacerbations assessed by the EXACT tool over 52 weeks **Symptom control** • Evaluation of clinical COPD respiratory symptoms using E-RS: COPD in the EXACT tool **Mortality** **AEs of treatment** • AEs/TEAEs • **MACE events** **HRQoL** • Change from baseline to Week 52 in SGRQ total score • Proportion of participants with an improvement in SGRQ score of ≥4 points (MCID) from baseline to Week 52	**Lung function** • Change from baseline in pre-BD FEV_1, post-BD FEV_1, FEF 25-75% and FVC • Annualised loss of lung function as assessed by a FEV_1 slope analysis • **FEV_1% predicted by GOLD stage at Week 52** *(post-hoc analysis)* **Incidence and severity of acute exacerbations** • Annualised rate of severe COPD exacerbations over the 52-week treatment period • Time to first moderate or severe COPD exacerbation during the 52-week treatment period • Time to first severe COPD exacerbation during the 52-week treatment period • Annualised rate of COPD exacerbations assessed by the EXACT tool over 52 weeks **Symptom control** • Evaluation of clinical COPD respiratory symptoms using E-RS: COPD in the EXACT tool **Mortality** **AEs of treatment** • AEs/TEAEs • **MACE events** **HRQoL** • Change from baseline to Week 52 in SGRQ total score • Proportion of participants with an improvement in SGRQ score of ≥4 points (MCID) from baseline to Week 52 • Change from baseline in EQ-5D-5L single index score at Week 24 and Week 52

Trial number (acronym)	BOREAS (NCT03930732)	NOTUS (NCT04456673)
Pre-planned subgroups	The primary (annualised rate of moderate[b] or severe[c] COPD exacerbations at Week 52) and key secondary (change from baseline to Week 12 in the pre-BD FEV_1) efficacy endpoints were analysed based on: Demographics • Age group (<65 or ≥65 years; 40-64, 65-74, 75-80 years) • Gender (Male or Female) • Race (White or non-White) • Ethnicity (Hispanic/Latino or Not Hispanic/Latino) • Region • Territory • Baseline weight (<70, ≥70 to <90, ≥90 kg; <60, ≥60 kg) • Baseline BMI (<25, ≥25 to <30, ≥30 kg/m^2) Disease characteristics • ICS dose level at baseline (high, non-high, or none) • ICS dose at baseline (<median or ≥median) • Smoking status at screening (current or former smokers) • Number of moderate or severe COPD exacerbation events within one year prior to Visit 1 (≤2, 3, or ≥4) • Number of severe COPD exacerbation events within one year prior to Visit 1 (0, 1, ≥2) • Baseline predicted post-BD FEV_1% (<50% or ≥50%) • Baseline pre-BD FEV_1 (< or ≥ median) • Baseline FEV_1 reversibility (<12%, ≥12%; < or ≥ median) Biomarkers • Baseline FeNO (<20, ≥20 ppb) • Baseline eotaxin-3 (< or ≥ median) • Baseline IgE (< 100 , ≥100 IU/ml) • Baseline PARC (< or ≥ median) • Baseline fibrinogen (<350, ≥350 mg/dL) • Maximum EOS counts during screening (≤0.3 to <0.5, ≥0.5 Giga/L)	The primary (annualised rate of moderate[b] or severe[c] COPD exacerbations at Week 52) and key secondary (change from baseline to Week 12 in the pre-BD FEV_1) efficacy endpoints were analysed based on: Demographics • Age group (<65 or ≥65 years; 40-64, 65-74, 75-80 years) • Gender (Male or Female) • Race (White or non-White) • Ethnicity (Hispanic/Latino or not Hispanic/Latino) • Region • Territory • Baseline weight (<70, ≥70 to <90, ≥90 kg; <60, ≥60 kg) • Baseline BMI (<25, ≥25 to <30, ≥30 kg/m^2) Disease characteristics • ICS dose level at baseline (high, non-high, or none) • ICS dose at baseline (<median or ≥median) • Smoking status at screening (current or former smokers) • Number of moderate or severe COPD exacerbation events within one year prior to Visit 1 (≤2, 3, or ≥4) • Number of severe COPD exacerbation events within one year prior to Visit 1 (0, 1, ≥2; 0, ≥1) • Baseline predicted post-BD FEV_1% (<50% or ≥50%) • Baseline pre-BD FEV_1 (< or ≥ median) • Baseline FEV_1 reversibility (<12%, ≥12%; < or ≥ median) • Ongoing emphysema at baseline (yes or no) • E-RS: COPD RS-Cough and Sputum (< or ≥ median) • Baseline BODE score (≤4 or >4) Biomarkers • Baseline FeNO (<20, ≥20 ppb) • Baseline eotaxin-3 (< or ≥ median)[d] • Baseline IgE (<100, ≥100 IU/ml) • Baseline PARC (< or ≥ median)[d] • Baseline fibrinogen (<350, ≥350 mg/dL) • Maximum EOS counts during screening (<0.5, ≥0.5 Giga/L)

Trial number (acronym)	BOREAS (NCT03930732)	NOTUS (NCT04456673)
Post-hoc subgroups	The primary (annualised rate of moderate[b] or severe[c] COPD exacerbations at Week 52) and key secondary (change from baseline to Week 12 in the pre-BD FEV_1) efficacy endpoints were analyses based on: • Ongoing emphysema at baseline (yes, no) • E-RS: COPD RS-Cough and Sputum (< or ≥ median) • Baseline BODE index score (low, high) Additionally, the primary efficacy endpoint was analysed based on: • Number of severe COPD exacerbation events within one year prior to Visit 1 (0, ≥1)	None

[a] Score range: mild (1) to severe (5) dyspnoea.
[b] Moderate exacerbations included those requiring systemic glucocorticoid treatment and/or antibiotic treatment. Two events were considered separate if occurred ≥14 days apart.
[c] Severe exacerbations included those requiring hospitalisation or emergency department observation >24 hours. Two events were considered separate if occurred ≥14 days apart.
[d] Analyses of baseline plasma eotaxin-3 and serum PARC were not performed at the time of the NOTUS interim analysis data cut-off date.
AE = adverse effect; BD = bronchodilator; BMI = body mass index; BODE = body mass index, airflow obstruction, dyspnoea, and exercise; COPD = chronic obstructive pulmonary disease; EOS = eosinophils; E-RS: COPD = Evaluating Respiratory Symptoms in COPD; EXACT = Exacerbations of Chronic Pulmonary Disease Tool; FEF = forced expiratory flow; FeNO = fractional exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 second; FVC = force vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HRQoL = health-related quality of life; ICS = inhaled corticosteroids; IgE = immunoglobulin E; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; MACE = major adverse cardiovascular event; MCID = minimal clinically important difference; MRC = Medical Research Council; PARC = pulmonary and activation-regulated chemokine; PDE-4 = phosphodiesterase 4; q2w = every two weeks; SC = subcutaneous; SABA = short-acting β_2-agonist; SGRQ = St. George's Respiratory Questionnaire; TEAE = treatment emergent adverse event
Source: Bhatt et al. 2023(168); Sanofi 2023 [Data on file] BOREAS CSR(170); Bhatt et al. 2024(169); Sanofi 2023 [Data on file] NOTUS CSR(171); Sanofi 2023 [Data on file] NOTUS SAP(172); Sanofi 2023 [Data on file] NOTUS amended CTP 03(173)

B.2.3.1.1. BOREAS (NCT03930732)

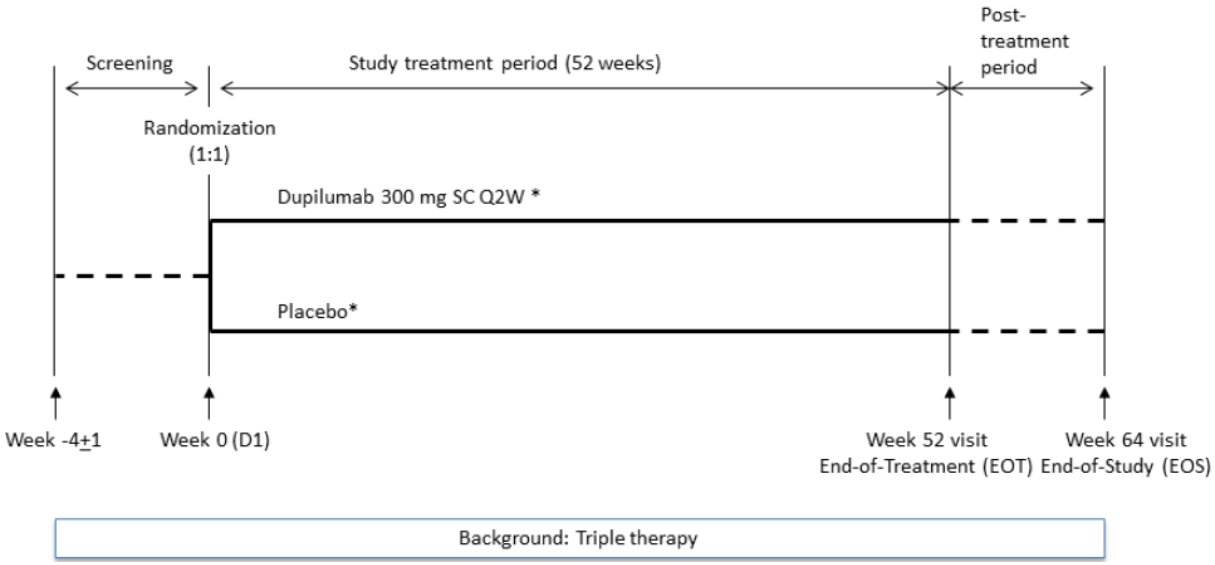
BOREAS was a phase 3, placebo-controlled, multinational, double-blind RCT designed to evaluate the efficacy, safety and tolerability of dupilumab in participants with COPD and Type 2 inflammation (blood EOS ≥300 cells/µL) who are uncontrolled (≥2 moderate or ≥1 severe historical exacerbations within 12 months) on LABA + LAMA + ICS (or LABA + LAMA if ICS was not appropriate).(168) Eligible participants were randomised 1:1 to receive subcutaneous (SC) dupilumab 300 mg or matching placebo once every two weeks (q2w) for 52 weeks, as add-on to background therapy (LABA + LAMA + ICS or LABA + LAMA if ICS was not appropriate).(168) Randomised participants in each treatment arm were stratified at baseline by ICS dose (high-dose, yes/no) and by country.(168) Enrolment of participants who were current smokers at screening was restricted to ≤30% of the total enrolled participants in the trial.(168) This was to ensure the distribution of current and former smokers in BOREAS was consistent with other large COPD RCTs and to prevent over-enrolment of active smokers.(168)

The study design is illustrated in Figure 12, with additional details provided in Appendix D.2. The BOREAS trial was conducted during the global COVID-19 pandemic (study start: May 2019; primary completion date: February 2023).(170) To ensure study continuity and protect participants' safety, contingency measures were introduced which allowed:(170)

- Implementation of temporary or alternative mechanisms for study visits and assessments, such as phone contact, virtual visits, online meetings, use of local clinic or laboratory locations, and home visits by skilled staff (as permitted per local regulation)
- Remote monitoring when on-site monitoring was not permitted.

No waivers to deviate from protocol enrolment criteria due to COVID-19 were granted and data integrity, participants' safety, study adherence and the scientific validity of BOREAS were not affected.(170)

Figure 12. Study design for BOREAS (NCT03930732)



*Dupilumab 300 mg Q2W was administered as one SC injection of dupilumab 300 mg (2 mL); placebo was administered as one SC injection of placebo matching dupilumab 300 mg (2 mL).
D= day; EOS = end-of-study; EOT = end-of treatment; SC = subcutaneous; q2w = every two weeks
Source: Sanofi 2023 [Data on file] BOREAS CSR(170)

B.2.3.1.2. NOTUS (NCT04456673)

NOTUS was a phase 3, placebo-controlled, multinational, double-blind RCT designed to evaluate the efficacy, safety and tolerability of dupilumab in participants with COPD and Type 2 inflammation (blood EOS ≥300 cells/µL) who are uncontrolled (≥2 moderate or ≥1 severe historical exacerbations within 12 months) on LABA + LAMA + ICS (or LABA + LAMA if ICS was not appropriate).(169) Treatment arms, randomisation criteria and the study design of NOTUS were the same as those described for BOREAS (Section B.2.3.1.1) with baseline smoking status as an additional randomisation stratification measure.(169)

The NOTUS trial was conducted during the global COVID-19 pandemic (study start: July 2020; primary completion date: September 2023).(171) To ensure study continuity and protect participants' safety, contingency measures were introduced which allowed:(171)

- Implementation of temporary or alternative mechanisms for study visits and assessments, such as phone contact, virtual visits, online meetings, use of local clinic or laboratory locations, and home visits by skilled staff (as permitted per local regulation)
- Remote monitoring when on-site monitoring was not permitted.

No waivers to deviate from protocol enrolment criteria due to COVID-19 were granted and data integrity, participants' safety, study adherence and the scientific validity of NOTUS were not affected.(171)

The NOTUS trial included a planned interim analysis with the goal of demonstrating efficacy prior to all patients completing the 52-week treatment period, given the high unmet medical need in this patient population (please refer to Section B.2.4 for further information on planned analyses).(169, 172) As NOTUS met its primary efficacy endpoint at the interim analysis, this was considered the primary efficacy analysis and all other multiplicity-controlled endpoints in the hierarchy were tested for statistical significance at α=0.05.(169) Overall, 70.2% of randomised participants in the dupilumab group and 71.6% of randomised participants in the placebo group completed the 52-week study intervention period, compared with 91.0% in the dupilumab group and 88.5% in the placebo group in BOREAS.(170, 171)

B.2.3.1.3. Pooled analysis of BOREAS and NOTUS

An integrated analysis of the efficacy and safety of dupilumab vs. placebo was performed based on pooled data from the final analysis of the BOREAS trial (Section B.2.4.1.4) and the interim analysis of the NOTUS trial (Section B.2.4.2.4).(174) The trials were designed as replicate studies such that the combined dataset could be analysed.

B.2.3.2. Baseline characteristics

B.2.3.2.1. BOREAS (NCT03930732)

Please refer to Appendix S for the individual baseline characteristics of the BOREAS trial. Baseline characteristics for the pooled analysis of BOREAS and NOTUS are presented below.

B.2.3.2.2. NOTUS (NCT04456673)

Please refer to Appendix S for the individual baseline characteristics of the NOTUS trial. Baseline characteristics for the pooled analysis of BOREAS and NOTUS are presented below.

B.2.3.2.3. Pooled analysis of BOREAS and NOTUS

The baseline characteristics for the pooled analysis of BOREAS and NOTUS are presented in Table 20 and were well balanced between the treatment arms.(174) In the randomised population (N=1,874), 80.6% of participants in the dupilumab group and 80.1% in the placebo arm completed the 52-week study intervention period, while 9.3% of participants in the dupilumab group and 9.9% in the placebo arm discontinued the study intervention period.(174) Overall, 9.9% of participants in both treatment arms were still ongoing in the 52-week study intervention period.(174) Information about patient disposition in the individual BOREAS and NOTUS trials is provided in Appendix D.2.

Table 20. Pooled analysis baseline characteristics

Baseline characteristics	**Dupilumab (n=938)**	**Placebo (n=936)**	**Total (N=1,874)**
Mean age (SD), years	65.1 (8.0)	65.0 (8.3)	65.1 (8.2)
Male, n (%)	618 (65.9)	634 (67.7)	1,252 (66.8)
Territory, n (%)[a]			
North America	105 (11.2)	106 (11.3)	211 (11.3)
European Union	366 (39.0)	367 (39.2)	733 (39.1)
Rest of the World	467 (49.8)	463 (49.5)	930 (49.6)
Race, n (%)			
White	815 (86.9)	813 (86.9)	1,628 (86.9)
Black/African Descent	7 (0.7)	10 (1.1)	17 (0.9)
Asian	74 (7.9)	70 (7.5)	144 (7.7)
American Indian/Alaskan Native	25 (2.7)	30 (3.2)	55 (2.9)
Native Hawaiian/other Pacific Islander	1 (0.1)	1 (0.1)	2 (0.1)
Multiple	14 (1.5)	8 (0.9)	22 (1.2)
Ethnicity, n (%)			
Hispanic or Latino	283 (30.2)	278 (29.7)	561 (29.9)
Not Hispanic or Latino	650 (69.3)	650 (69.4)	1,300 (69.4)
Unknown	1 (0.1)	2 (0.2)	3 (0.2)
Smoking status, n (%)			
Current smoker	276 (29.4)	282 (30.1)	558 (29.8)
Former smoker	662 (70.6)	654 (69.9)	1,316 (70.2)
Smoking quantity; mean (SD), pack-years[b]	39.03 (23.06)	41.79 (27.71)	40.40 (25.50)
BMI; mean (SD), kg/m^2	27.80 (5.37)	27.71 (5.64)	27.76 (5.51)
Background medication, n (%)			
Baseline high-dose ICS	258 (27.5)	260 (27.8)	518 (27.6)
Triple therapy (LABA + LAMA + ICS)	921 (98.2)	919 (98.2)	1,840 (98.2)
Biomarkers of Type 2 inflammation			
Screening maximum EOS level; mean (SD) (giga/L)[c]	0.53 (0.32)	0.53 (0.32)	0.53 (0.32)
Baseline blood EOS count; mean (SD) (giga/L)[c]	0.40 (0.31)	0.40 (0.32)	0.40 (0.32)
Baseline FeNO; mean (SD), ppb	24.97 (25.67)	23.92 (22.68)	24.44 (24.22)
Pre-BD FEV_1; mean (SD), L[d]	1.32 (0.47)	1.35 (0.48)	1.33 (0.48)

Baseline characteristics	Dupilumab (n=938)	Placebo (n=936)	Total (N=1,874)
Pre-BD FEV_1; mean (SD), % predicted[d]	46.75 (13.29)	47.57 (13.09)	47.16 (13.19)
Post-BD FEV_1; mean (SD), L[e]	1.41 (0.48)	1.44 (0.49)	1.42 (0.48)
Post-BD FEV_1; mean (SD), % predicted[e]	50.03 (12.93)	50.65 (12.77)	50.34 (12.85)
Post-BD FEV_1/FVC; mean (SD), L[e]	0.49 (0.12)	0.49 (0.12)	0.49 (0.12)
Pre-BD $FEF_{25-75\%}$; mean (SD), L/s[d]	0.52 (0.34)	0.53 (0.33)	0.52 (0.33)
FEV_1 reversibility; mean (SD), %[f]	8.52 (12.78)	8.18 (11.98)	8.35 (12.39)
SGRQ score, mean (SD)[g]	50.18 (17.35)	49.75 (17.22)	49.96 (17.28)
E-RS: COPD total score, mean (SD)[h,i]	13.2 (7.0)	13.1 (7.1)	13.1 (7.0)
EQ-5D-5L score, mean (SD)	0.710 (0.190)	0.714 (0.195)	0.712 (0.192)
Moderate or severe exacerbations in 1 year prior to screening, n (%)[j]			
1	117 (12.5)	105 (11.2)	222 (11.8)
2	634 (67.6)	646 (69.0)	1,280 (68.3)
≥3	186 (19.8)	185 (19.8)	371 (19.8)
Severe exacerbations in 1 year prior to screening, n (%)[c,f]			
1	198 (21.1)	181 (19.3)	379 (20.2)
>1	44 (4.7)	33 (3.5)	77 (4.1)

Note: numbers have been rounded and might not sum to 100.
[a] North America: Canada and United States; European Union: Belgium, Poland, Bulgaria, Spain, France, Portugal, Germany, Netherlands, Lithuania, Latvia, Greece, United Kingdom, Czech Republic, Slovakia, Hungary, Romania, Sweden, Italy, Finland, Denmark; Rest of World: Australia, South Africa, Argentina, Chile, Colombia, Peru, Brazil, Mexico, Russia, Ukraine, Serbia, Israel, Japan, China, South Korea, Turkey.
[b] The smoking quantity analysis included 1,701 participants; 859 in the dupilumab arm and 842 in the placebo arm.
[c] The maximum EOS levels at screening, baseline blood EOS count, and severe exacerbations in 1 year prior to screening analyses included 1,873 participants; 937 in the dupilumab arm and 936 in the placebo arm.
[d] The pre-BD FEV_1 and $FEF_{25-75\%}$ analyses included 1,872 participants; 936 in the dupilumab arm and 936 in the placebo arm.
[e] The post-BD FEV_1 and FEV_1/FVC analyses included 1,870 participants; 935 in the dupilumab arm and 935 in the placebo arm.
[f] The FEV_1 reversibility analysis included 1,869 participants; 934 in the dupilumab arm and 935 in the placebo arm.
[g] The SGRQ score analysis included 1,827 participants; 917 in the dupilumab arm and 910 in the placebo arm.
[h] The E-RS: COPD score uses the 11 respiratory symptom items of the EXACT score. More severe respiratory symptoms are characterised by higher E-RS: COPD scores.
[I] The E-RS: COPD score analysis included 1,851 participants: 924 in the dupilumab arm and 927 in the placebo arm.
[j] Moderate exacerbations included exacerbations requiring systemic glucocorticoid treatment and/or antibiotic treatment. Severe exacerbations included those requiring hospitalisation, emergency department/urgent care facility visit longer than 24 hours or resulting in death. Two events were considered separate if they occurred ≥14 days apart.
BD = bronchodilator; BMI = body-max index; COPD = chronic obstructive pulmonary disease; EOS = eosinophil; EQ-5D-5L = EuroQoL 5-dimension 5-level; E-RS: COPD = Evaluating Respiratory Symptoms in COPD; EXACT = Exacerbations of Chronic Pulmonary Disease Tool; FEF = forced expiratory flow; FeNO = fractional exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; ICS = inhaled corticosteroids; LABA = long-acting β2-agonist; LAMA = long-acting muscarinic antagonist; ppb = parts per billion; SD = standard deviation; SGRQ = St. George's Respiratory Questionnaire
Source: Sanofi 2023 (Data on file) Pooled analysis summary of clinical efficacy(174)

B.2.3.3. Expert elicitation

An advisory board was held in July 2024 with five experienced UK clinical experts (including respiratory physicians and experts in respiratory epidemiology and respiratory medicine) and two health economists.(167) Key objectives included validation of the clinical assumptions and inputs for the cost-effectiveness model as well as the model structure.(167) Experts were selected based on their experience in the therapy area and to represent a range of treatment centres.(167) Questions and answers were shared by all attendees via an online platform over a 5-day period, with a virtual meeting taking place over 2.5 hours to summarise insights and

clarify specific points where consensus was not reached.(167) Transcripts from the online platform and virtual call were synthesised into a summary report, which has been provided with the submission.(167)

Additionally, between June and September 2024, Sanofi undertook a structured expert elicitation (SEE) exercise with seven clinicians in total with experience of dupilumab in clinical practice from different centres in England. The objective was to consolidate clinical opinions on how long the FEV_1 benefits observed in the BOREAS and NOTUS trials might be maintained outside the confines of the studies before natural FEV_1 decline might be expected to resume, in order to inform the FEV_1 treatment effect period in the model (Section B.3.3.6.1). Further information on the SEE is provided in Appendix P.

B.2.3.4. Real-world evidence

No Sanofi-led real-world studies assessing dupilumab effectiveness according to its licensed COPD indication(1) have been completed to date. However, a recent independent pre-proof publication has assessed the long-term real-world efficacy of dupilumab in patients with comorbid COPD.(175) Note that these data are not derived from a Sanofi-led study, have not been used to support the clinical efficacy of dupilumab in this submission, nor have they been used as inputs in the cost-effectiveness model, given the COPD population addressed in the study is significantly different to the population defined in this submission. We have provided a summary of this real-world study for completeness.

A US population-based cohort study included 346,338 patients with COPD, of whom 1,521 had received dupilumab treatment for other Type 2 inflammatory conditions excluding asthma (i.e., AD, EoE, CRSwNP, PN).(175) Dupilumab-treated patients with COPD were propensity score-matched to 1,521 non-treated controls, with COPD outcomes compared over a mean period of 80.1 ± 75.2 weeks for the dupilumab group and 134.6 ± 116.2 weeks for the control group. Dupilumab was associated with a significantly lower risk of:(175)

- All-cause mortality (HR: 0.53; 95% CI: 0.43, 0.65)
- Emergency room visits (HR: 0.78; 95% CI: 0.69, 0.89)
- AEs (HR: 0.59; 95% CI: 0.53, 0.65)
- New-onset pneumonia (HR: 0.65; 95% CI: 0.50, 0.86)
- New-onset acute respiratory failure (HR: 0.57; 95% CI: 0.44, 0.73)
- New-onset acute respiratory distress syndrome (ARDS) (HR: 0.36; 95% CI: 0.22, 0.58)
- New-onset heart failure (HR: 0.69; 95% CI: 0.53, 0.90)
- New onset anxiety (HR: 0.70; 95% CI: 0.53, 0.93).

As the article is in proof stage at the time of making this submission it has not been possible for us to review the methodology and so overall the inclusion criteria are unclear as are patient characteristics in terms of exacerbation history and background therapy. The time range for the study is from 2017-2024 during which there was no licence for COPD and in the earlier part of the study, no data supporting the use of dupilumab in any respiratory disease. Therefore, we urge caution in the interpretation of these results. However, this study

provides the first published real-world evidence of dupilumab effectiveness in COPD, albeit in a population characteristically different from that of BOREAS, NOTUS, or that defined by the licensed COPD indication.(1)

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

A summary of the statistical analyses performed in the BOREAS and NOTUS trials is provided in Table 21, with further information presented in the following sections. Details of participant flow in each trial are provided in Appendix D.2.

Table 21. Summary of statistical analyses

Trial number (acronym)	Hypothesis	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
BOREAS (NCT03930732)	Null hypothesis: No treatment difference between dupilumab and placebo in annualised rate of COPD exacerbation. Alternative hypothesis: There is a treatment difference between dupilumab and placebo in annualised rate of COPD exacerbation.	The primary analysis was conducted using the ITT population. Analysis of the primary endpoint was performed using a negative binomial regression model (response variable: total number of events occurring over the 52-week treatment period; covariates: treatment group, region (pooled country), dose of ICS at baseline, smoking status at screening, disease severity at baseline, and number of moderate or severe exacerbation events of COPD ≤1 year before trial enrolment). Log-transformed observation duration was used as offset variable.	The sample size was based on power calculations for the primary endpoint. It was calculated that 462 participants in each trial arm were required to detect a 25% relative risk reduction, with 90% power at a 2-sided significance level of α=0.05 (the final alpha was reduced to 0.049 as a result of the planned interim analysis).	Exacerbations were confirmed by an independent adjudication committee and recorded in an eCRF. The analysis only included adjudicated exacerbations. Participants who discontinued treatment continued to be monitored and off-treatment exacerbations up to Week 52 were included in the analysis. For participants that withdrew from study earlier than Week 52, the analysis included all observed exacerbations until the last contact date. No imputation was performed for the unobserved events that may have occurred after study discontinuation and up to Week 52.
NOTUS (NCT04456673)	As above	As above	As above	As above

COPD = chronic obstructive pulmonary disease; eCRF = electronic case report form; ITT = intention-to-treat
Source: Bhatt et al. 2023(168); Bhatt et al. 2024(169)

B.2.4.1. BOREAS (NCT03930732)

B.2.4.1.1. Study population and sample size

The BOREAS trial enrolled participants aged 40 to 80 years with uncontrolled COPD (≥2 moderate or ≥1 severe historical exacerbations within 12 months) and Type 2 inflammation (blood EOS ≥300 cells/µL) who were receiving triple therapy (LABA + LAMA + ICS; or LABA + LAMA if ICS was not appropriate).(168) The sample size was based on the primary efficacy endpoint of annualised rate of moderate or severe COPD exacerbations over 52 weeks of treatment.(168) It was calculated that 462 participants in each trial arm were required to detect a 25% relative risk reduction (i.e., annualised rate of 1.125 for the dupilumab group) with 90% power at a 2-sided significance level α=0.049 (a 0.001 administrative penalty was applied to the final analysis as a result of the planned interim analysis; Section B.2.4.1.4).(168)

B.2.4.1.2. Patient populations analysed

Efficacy analyses were conducted using the intention-to-treat (ITT) population, defined as all randomised participants according to the treatment arm a participant was randomly allocated.(168)

Safety analyses were conducted using the safety population, defined as all participants who received ≥1 partial or full dupilumab or placebo dose, according to the treatment participants actually received.(168) The safety population included:

- Non-randomised but treated participants
- Randomised patients for whom it was unclear whether they took the study drug
- For patients on placebo who were accidentally exposed to dupilumab, the treatment group allocation for the as-treated analysis was the dupilumab group
- For patients on dupilumab who accidentally received placebo, the actual treatment group allocation for the as-treated analysis was the dupilumab group.

B.2.4.1.3. Statistical analyses

A negative binomial model was used for the analysis of the primary endpoint of annualised rate of moderate or severe COPD exacerbations over 52 weeks of treatment.(168) In the model, the total number of events occurring over the 52-week treatment period was used as a response variable with the following covariates: dose of ICS at baseline, geographic region (pooled according to country), number of moderate or severe exacerbation events of COPD ≤1 year before trial enrolment, physician-assessed disease, severity at baseline, smoking status at screening, and the trial group.(168) The log-transformed observation duration (defined as from randomisation to Visit 16 [Week 52]) was used as the offset variable.(168)

The statistical analyses used to evaluate the secondary endpoints are summarised in Table 22.(168)

Table 22. Summary of statistical analyses for secondary endpoints in BOREAS

Category	Endpoint	Population	Intercurrent event(s) handling strategy and missing data handling	Population-level summary
Continuous	Change from baseline in pre-BD FEV_1 at Weeks 2, 4, 8, 12, 24, 36, 44 and 52 Change from baseline in SGRQ at Week 52 Change from baseline in post-BD FEV_1 at Weeks 2, 4, 8, 12, 24, 36 and 52 Change from baseline in FEF 25-75% at Weeks 2, 4, 8, 12, 24, 36, 44 and 52	ITT	Intercurrent events handling: • Discontinuing the study intervention prior to Week 12 or Week 52: all data collected after discontinuation were used in the analysis (treatment policy strategy) Missing data imputation rules: • Missing data were imputed latently by MMRM based on missing at random assumption	MMRM model using change from baseline in corresponding endpoint values up to corresponding weeks as response variables, and factors for the following items as covariates: • Treatment group • Age[a] • Sex[a] • Height[a] • Region (pooled country) • ICS dose at baseline • Smoking status at screening • Visit • Treatment-by-visit interaction • Baseline value of the endpoint • Baseline-by-visit interaction
Proportion	Proportion of SGRQ improvement (≥4 points) at Week 52	ITT	Intercurrent events handling: • Discontinuation of study intervention prior to Week 52: Off-study intervention data were included in the analysis (treatment policy strategy) Missing data imputation rules: • Having missing data at Week 52: Participants were considered as non-responders	Logistic regression model, with the following covariates: • Treatment group • Region (pooled country) • ICS dose at baseline • Smoking status at screening • Baseline SGRQ total score
Event	Annualised rate of severe COPD exacerbations over the 52-week treatment period	ITT	Intercurrent events handling: • Discontinuation of study treatment before Week 52: Off-study treatment data up to Week 52 were included in the analysis (treatment policy strategy) Missing data imputation rules: Discontinuing the study follow-up before Week 52: Analyses were censored at the time of study discontinuation	Negative binomial regression model using the total number of events that occurred during the 52-week planned treatment period as the response variable and the following as covariates: • Treatment group • Region (pooled country) • ICS dose at baseline • Smoking status at screening • Baseline disease severity • Number of moderate or severe COPD exacerbation events

Category	Endpoint	Population	Intercurrent event(s) handling strategy and missing data handling	Population-level summary
				within one year prior to the study Log-transformed observation duration was used as offset variable
Time-to-event	Time to first moderate or severe COPD exacerbation during the 52-week treatment period	ITT	Intercurrent events handling: • Discontinuation of study intervention before Week 52: Off-study intervention data up to Week 52 were included in the analysis (treatment policy strategy) Missing data imputation rules: • Discontinuing the study follow-up before Week 52: Analyses were censored at the time of study discontinuation	Cox proportional hazards model using the time to the first event as the dependent variable with the following covariates: • Treatment group • Region (pooled country) • ICS dose at baseline • Smoking status at screening • Baseline disease severity • Number of moderate or severe COPD exacerbation events within one year prior to the study

[a] Age, sex and height are only included for spirometry endpoints analyses.
BD = bronchodilator; COPD = chronic obstructive pulmonary disease; FEF = forced expiratory flow; FeNO = fractional exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; ITT = intent-to-treat; MMRM = mixed-effect model with repeated measure; SGRQ = St. George's Respiratory Questionnaire
Source: Bhatt et al. 2023(168)

Primary and selected secondary/exploratory endpoints were tested based on a hierarchical order (as listed below) to control for type I error at a 2-sided significance level of α=0.05:(168)

- Annualised rate of moderate or severe exacerbations of COPD over the 52-week treatment period (primary endpoint)
- Change in pre-BD FEV_1 from baseline to Week 12
- Change in pre-BD FEV_1 from baseline to Week 52
- Change in pre-BD FEV_1 from baseline to Week 12 in patients with baseline FeNO ≥20 ppb
- Change in pre-BD FEV_1 from baseline to Week 52 in patients with baseline FeNO ≥20 ppb
- Change in SGRQ total score from baseline to Week 52
- Proportion of patients with SGRQ total score improvement ≥4 points at Week 52
- Change in E-RS–COPD total score from baseline to Week 52
- Annualised rate of moderate or severe exacerbations of COPD in patients with a baseline FeNO ≥20 ppb.

The statistical analysis methods for patient subgroups are described in Section B.2.7.

B.2.4.1.4. Planned analyses

BOREAS included three planned analyses:(168, 170)

- A non-binding futility interim analysis when the first 408 randomised patients completed or discontinued prior to Week 12.
    - The purpose of the interim analysis was to gain an early understanding of the benefit-risk profile of dupilumab in the target population.
    - The interim analysis was performed by independent statisticians and unblinded results were reviewed by the data monitoring committee (DMC), who recommended action based on the non-binding futility criterion specified in the DMC charter and statistical analysis plan.
- A final analysis of all data collected by the time the last participant had completed Week 52 or the last participant had discontinued from the study before Week 52.
    - Due to the planned interim analysis, an administrative penalty of 0.001 was taken from the significance level used at the final analysis (i.e., two-sided α=0.049 was used for the final analysis).
- Cumulative analysis of all data collected from Week 0 up to Week 64 (i.e., all data collected from study start until study end, including the 12-week post-intervention follow-up period).
    - Upon completion or early discontinuation of the 52-week treatment period, participants entered a 12-week post-intervention follow-up period (Week 52 to 64).
    - Cumulative analyses for efficacy endpoints related to COPD exacerbations, spirometry and SGRQ, as well as safety, were performed from Week 0 up to Week 64. Data on E-RS: COPD and COPD exacerbations assessed by the EXACT tool were not collected during the 12-week post-intervention follow-up period.

B.2.4.1.5. Participant flow

Detailed information on participant flow in the BOREAS trial is provided in Appendix D.2, including the consort diagram.

B.2.4.2. NOTUS (NCT04456673)

B.2.4.2.1. Study population and sample size

The NOTUS trial enrolled participants aged 40 to 85 years with uncontrolled COPD (≥2 moderate or ≥1 severe historical exacerbations within 12 months) and Type 2 inflammation (blood EOS ≥300 cells/µL) who were receiving triple therapy (LABA + LAMA + ICS; or LABA + LAMA if ICS was not appropriate).(169) Sample size calculations were the same as those reported for BOREAS (Section B.2.4.1.1).(169)

B.2.4.2.2. Patient populations analysed

The analysis populations in NOTUS were defined the same as those in the BOREAS trial (Section B.2.4.1.2).(169, 172)

B.2.4.2.3. Statistical analyses

The statistical analyses (including the hierarchical testing procedure) used to evaluate the primary and secondary endpoints in NOTUS were the same as those in the BOREAS trial (Section B.2.4.1.3).(172) The statistical analysis methods for patient subgroups are described in Section B.2.7.

B.2.4.2.4. Planned analyses

NOTUS included two planned analyses:(169, 172)

- An interim analysis when the information fraction was ≥0.92 based on follow-up time of the ITT population for the primary endpoint.
    - The purpose of the interim analysis was to try and demonstrate efficacy when ≥92% of the information fraction for the primary endpoint was available, but prior to all patients completing the 52-week treatment period, as COPD is a disease with a high unmet medical need.
    - A hierarchical testing procedure was used for testing primary, key secondary and other endpoints. As the primary endpoint demonstrated efficacy at the interim analysis based on the alpha allocated, the rest of the multiplicity-controlled endpoints were tested with α=0.05 and the interim analysis database lock was considered the primary analysis for all endpoints.
    - The hierarchical order was the same as that in BOREAS (Section B.2.4.1.3)
- A final analysis of all data collected up until the end-of the study.
    - The database lock for the final analysis is planned when all patients complete the Week 52 visit or discontinue from the study before Week 52 but may occur when all patients complete the Week 64 visit or discontinue from the study.

B.2.4.2.5. Participant flow

Detailed information on participant flow in the NOTUS trial is provided in Appendix D.2, including the consort diagram.

B.2.4.3. Pooled analysis of BOREAS and NOTUS

B.2.4.3.1. Study population and sample size

The integrated analysis was based on pooled data from the final analysis of the BOREAS trial (Section B.2.4.1.4) and the interim analysis of the NOTUS trial (Section B.2.4.2.4).(174) In total, 938 participants randomised to dupilumab and 936 participants randomised to placebo were included in the integrated summary of efficacy, while 938 participants randomised to dupilumab and 934 participants randomised to placebo were included in the integrated summary of safety.(174)

B.2.4.3.2. Patient populations analysed

Efficacy analyses were conducted using the pooled ITT population, defined as all randomised participants according to the treatment arm a participant was randomly allocated.(176)

Safety analyses were conducted using the pooled safety population, defined as all randomised participants who received ≥1 dose of dupilumab or placebo, according to the treatment participants actually received.(177)

B.2.4.3.3. Statistical analyses

Efficacy endpoints, primary estimands and data handling procedures were the same as those used in the individual studies (Section B.2.4.1.3 and Section B.2.4.2.3).(176) There was no multiplicity adjustment and no hierarchical testing procedure for the pooled efficacy analysis, therefore p values are described as nominal.(174, 176)

B.2.4.3.4. Planned analyses

Only one analysis was planned based on pooled data from the final analysis of the BOREAS trial and the interim analysis of the NOTUS trial.(174)

B.2.4.3.5. Participant flow

Detailed information on participant flow in the BOREAS and NOTUS trials is provided in Appendix D.2, including the consort diagrams.

B.2.5. Critical appraisal of the relevant clinical effectiveness evidence

Study results published in a peer-reviewed journal were used as the primary source of data where available; clinical study reports (CSRs) were used as additional data sources as needed.

B.2.5.1. Quality assessment

The quality of the BOREAS and NOTUS trials was assessed using the Cochrane Risk of Bias Assessment Tool 2.0,(178) in line with recommendations from NICE and good practice guidelines. Overall, the risk of bias was considered low for both trials (Table 23).

Table 23. Quality assessment results for BOREAS and NOTUS

Bias domain	Risk of bias judgement	
	BOREAS (NCT03930732)(168)	**NOTUS (NCT04456673)(169)**
Bias arising from the randomisation process	Low	Low
Bias due to deviations from intended interventions	Low	Low
Bias due to missing outcome data	Low	Low*
Bias in measurement of the outcome	Low	Low
Bias in selection of the reported result	Low	Low
Overall risk of bias	**Low**	**Low**

* It is possible that there may be a risk of bias in some secondary and exploratory endpoints in the NOTUS study since ~70% of randomised participants completed the 52-week study intervention period, compared with ~90% in BOREAS. This was because the trial was stopped at the planned interim analysis as the primary efficacy endpoint was met (as described in Appendix S).

B.2.5.2. Applicability of the study results to clinical practice in England

BOREAS and NOTUS recruited patients globally, including 12 patients from 11 sites in England.(168, 169, 174) The majority of patients (98.2%) received triple background therapy,(174) consistent with the NICE 2019 guidelines which recommend escalation to triple inhaled therapies for patients with COPD who continue to experience limiting symptoms and exacerbations despite all other pharmacological and non-pharmacological interventions (Section B.1.3.2.2).(7)

Key demographic and disease characteristics in the BOREAS and NOTUS trials (including age, gender distribution, GOLD stage at baseline, proportion of patients with EOS ≥500 cells/μL) were similar to those observed in the Sanofi-led HES-CPRD study (described in Section B.1.3.1.3), indicating that the trial populations are similar to the population of patients with uncontrolled COPD and Type 2 inflammation in England.(59) Clinical experts in England consulted by Sanofi as part of an advisory board meeting in July 2024 confirmed that the patient eligibility criteria in the BOREAS and NOTUS trials, and the baseline demographics of recruited patients, are applicable and appropriate for the subpopulation of COPD patients in the UK who are frequent exacerbators (uncontrolled) with

raised EOS levels (Type 2 inflammation).(167) Therefore, the results of BOREAS and NOTUS are expected to be applicable to patients in routine clinical practice in England.

B.2.6. Clinical effectiveness results of the relevant studies

Primary and key secondary outcomes for the individual BOREAS and NOTUS trials as well as the pooled analysis are summarised in Table 24. For detailed results of the individual BOREAS and NOTUS trials please see Appendix S.

In BOREAS, statistically significant and clinically meaningful between-group differences were reached for all endpoints in the hierarchical testing procedure.(168, 170) In NOTUS, statistically significant and clinically meaningful between-group differences were reached for the primary and first three key secondary endpoints in the hierarchical testing procedure; after this point the hierarchical testing procedure broke and only nominal p values are provided for the subsequent multiplicity-controlled endpoints.(169, 171) There was no multiplicity adjustment and no hierarchical testing procedure for the pooled efficacy analysis, therefore p values are described as nominal.(174, 176)

Table 24. Summary of clinical effectiveness (ITT population)

Outcome	BOREAS (NCT03930732; N=939)		NOTUS (NCT04456673; N=935)		Pooled analysis (N=1,874)	
	Dupilumab (n=468)	Placebo (n=471)	Dupilumab (n=470)	Placebo (n=465)	Dupilumab (n=938)	Placebo (n=936)
Primary endpoint: Annualised rate of moderate or severe exacerbations of COPD over the 52-week treatment period						
Adjusted annualised rate of moderate or severe exacerbations, events per year (95% CI)	0.78 (0.64, 0.93)	1.10 (0.93, 1.30)	0.86 (0.70, 1.06)	1.30 (1.05, 1.60)	0.79 (0.69, 0.92)	1.16 (1.01, 1.33)
Rate ratio vs. placebo (95% CI)	0.70 (0.58, 0.86); p=0.0005		0.66 (0.54, 0.82); p=0.0002		0.69 (0.60, 0.79); nominal p<0.0001	
Unadjusted annualised rate of moderate or severe exacerbations, events per year	0.65	0.93	0.62	0.84	0.63	0.89
Key secondary endpoint: Change in pre-BD FEV_1 from baseline to Week 12						
LS mean change (SE), litres	0.160 (0.018)	0.077 (0.018)	0.139 (0.017)	0.057 (0.017)	0.147 (0.013)	0.064 (0.013)
LS mean difference vs. placebo (95% CI), litres	0.083 (0.042, 0.125); p<0.0001		0.082 (0.040, 0.124); p=0.0001		0.083 (0.053, 0.112); nominal p<0.0001	
Key secondary endpoint: Change in pre-BD FEV_1 from baseline to Week 52						
LS mean change (SE), litres	0.153 (0.019)	0.070 (0.019)	0.115 (0.021)	0.054 (0.020)	0.133 (0.015)	0.059 (0.015)
LS mean difference vs. placebo (95% CI), litres	0.083 (0.038, 0.128); p=0.0003		0.062 (0.011, 0.113); p=0.0182		0.073 (0.040, 0.107); nominal p<0.0001	
Key secondary endpoint: Change in SGRQ total score from baseline to Week 52						
LS mean change (SE)	−9.7 (0.8)	−6.4 (0.8)	−9.8 (0.9)	−6.4 (0.9)	−9.9 (0.6)	−6.6 (0.6)
LS mean difference vs. placebo (95% CI)	−3.4 (−5.5; −1.3); p=0.0017		−3.4 (−5.8, −0.9); p=0.0068		−3.4 (−5.0, −1.8); nominal p<0.0001	
Key secondary endpoint: SGRQ total score improvement ≥4 points at Week 52						
Percentage of patients	51.5	43.1	51.4	46.5	51.4	44.6
Odds ratio vs. placebo (95% CI)	1.4 (1.1, 1.9); p=0.0089		1.2 (0.9, 1.6); nominal p=0.3329		1.3 (1.1, 1.6); nominal p=0.0089	

BD = bronchodilator; CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; ITT = intention-to-treat; LS = least squares; SE = standard error; SGRQ = St. George's Respiratory Questionnaire

Source: Bhatt et al. 2023(168); Sanofi 2023 [Data on file] BOREAS CSR(170); Bhatt et al. 2024(169); Sanofi 2023 [Data on file] NOTUS CSR(171); Sanofi 2023 [Data on file] Pooled analysis summary of clinical efficacy(174)

B.2.6.1. BOREAS (NCT03930732)

Please refer to Appendix S for the individual results of the BOREAS trial. Results of the pooled analysis of BOREAS and NOTUS are presented below.

B.2.6.2. NOTUS (NCT04456673)

Please refer to Appendix S for the individual results of the NOTUS trial. Results of the pooled analysis of BOREAS and NOTUS are presented below.

B.2.6.3. Pooled analysis of BOREAS and NOTUS

The clinical effectiveness data presented in this section and subsequently used in the cost-effectiveness modelling are based on the pooled analysis of BOREAS and NOTUS.(174, 179)

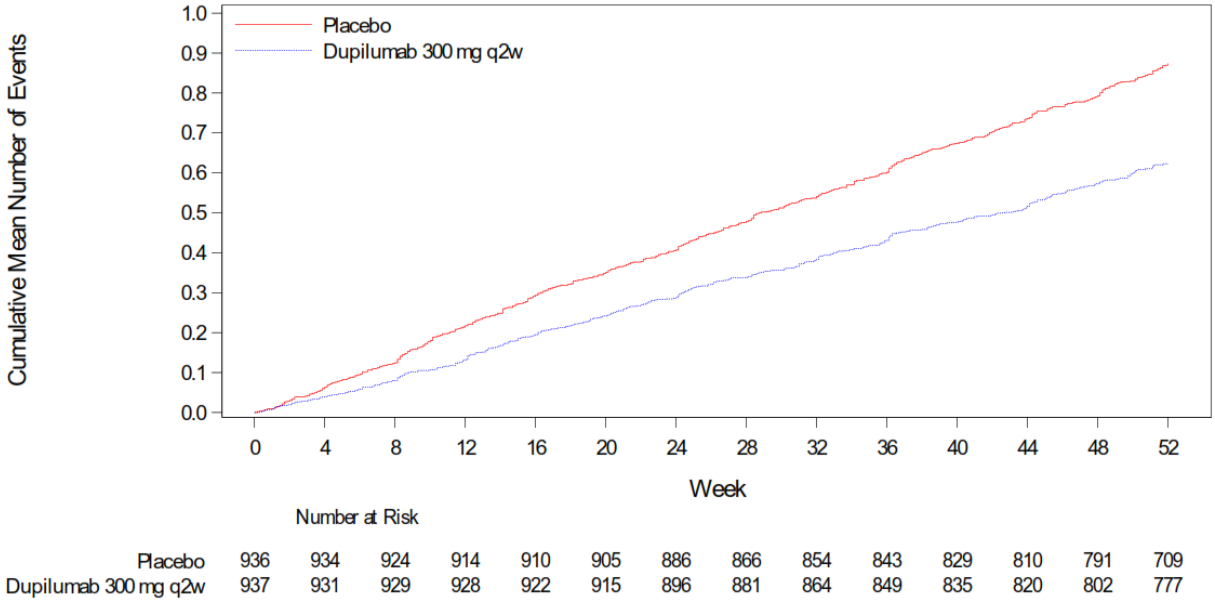
B.2.6.3.1. Efficacy

Primary endpoint: Annualised rate of moderate or severe exacerbations of COPD over the 52-week treatment period

Dupilumab resulted in a clinically meaningful reduction of 31% in the annualised rate of moderate or severe exacerbations compared to placebo in patients with uncontrolled COPD despite background therapy (rate ratio: 0.69; 95% CI: 0.60, 0.79; nominal p<0.0001).(174) The adjusted annualised rate of moderate or severe COPD exacerbations was 0.79 (95% CI: 0.69, 0.92) in participants receiving dupilumab compared to 1.16 (95% CI: 1.01, 1.33) in participants receiving placebo.(174)

A reduction in the cumulative mean number of moderate or severe COPD exacerbation events with dupilumab compared to placebo was observed as early as Week 4 and the difference progressively increased up to Week 52 (Figure 13).(174)

Figure 13. Pooled analysis cumulative mean number of moderate or severe COPD exacerbations during the 52-week treatment period (pooled ITT population)



COPD = chronic obstructive pulmonary disease; ITT = intention-to-treat; q2w = every two weeks
Source: Sanofi 2023 [Data on file] Pooled analysis summary of clinical efficacy appendix(179)

The overall number of moderate or severe COPD exacerbation events during the 52-week treatment period was lower with dupilumab compared to placebo (559 events vs. 774 events; Table 25).(174) The majority of COPD exacerbation events in both treatment arms were moderate and required treatment with both systemic antibiotics and corticosteroids.(174) The number of severe COPD exacerbation events was low in both treatment arms.(174)

Table 25. Pooled analysis summary of moderate or severe COPD exacerbations during the 52-week treatment period (pooled ITT population)

	Dupilumab (n=938)	Placebo (n=936)
Total number of moderate or severe events, n	559	774
Number of severe events, n	54	76
Requiring hospitalisation, n (%)	53 (98.1)	75 (98.7)
Requiring emergency medical care visit, n (%)	1 (1.9)	1 (1.3)
Resulting in death, n (%)	0	0
Number of moderate events, n	505	698
Requiring use of systemic corticosteroid medications only, n (%)	154 (30.5)	237 (34.0)
Rate ratio vs. placebo (95% CI)[a]	Not available	
Requiring use of systemic antibiotics only, n (%)	92 (18.2)	124 (17.8)
Rate ratio vs. placebo (95% CI)[a]	Not available	
Requiring use of both systemic corticosteroid medications and systemic antibiotics, n (%)	259 (51.3)	337 (48.3)
Rate ratio vs. placebo (95% CI)[a]	Not available	

	Dupilumab (n=938)	Placebo (n=936)
Treated with systemic antibiotics (with or without corticosteroids), n (%)	351 (69.5)	461 (66.0)
Rate ratio vs. placebo (95% CI)[a]	Not available	

CI = confidence interval; COPD = chronic obstructive pulmonary disease; ITT = intention-to-treat
Note: Included are all adjudicated moderate or severe exacerbation event (whether the participant was on treatment or not) occurring during the 52-week treatment period; The number of events was used as the denominator for the calculation of percentages.
Source: Sanofi 2023 [Data on file] Pooled analysis summary of clinical efficacy(174)

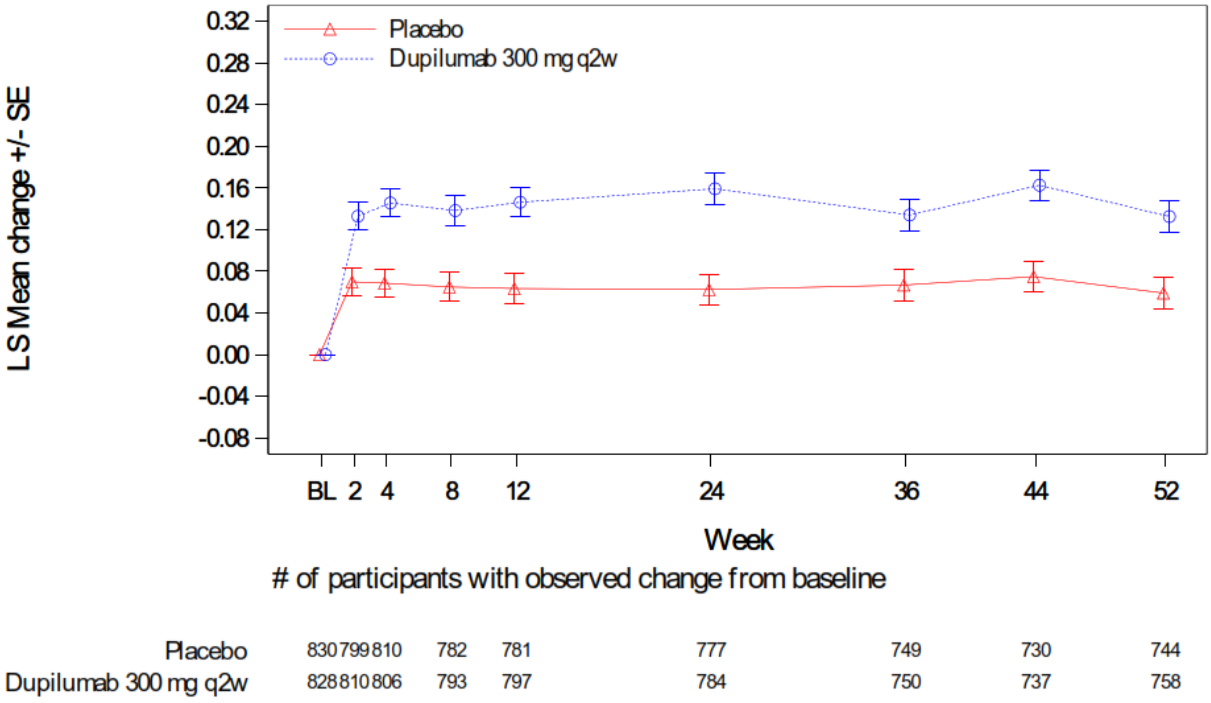
Key secondary endpoint: Change in pre-BD FEV_1 from baseline to Week 12 and Week 52

Dupilumab led to early and sustained improvements in pre-BD FEV_1 compared to placebo (Figure 14).(174)

At Week 12, the LS mean change from baseline in pre-BD FEV_1 was greater with dupilumab compared to placebo (147 ml vs. 64 ml; LS mean difference: +83 ml; 95% CI: 53, 112; nominal p<0.0001).(174) The improvement in LS mean change from baseline in pre-BD FEV_1 with dupilumab over placebo was maintained through Week 52 (133 ml vs. 59 ml; LS mean difference: +73 ml; 95% CI: 40, 107; nominal p<0.0001).(174)

The benefit of dupilumab over placebo on pre-BD FEV_1 was observed as early as Week 2 after initiating treatment (Figure 14).(174)

Figure 14. Pooled analysis LS mean change from baseline in pre-BD FEV_1 (L) up to Week 52 (pooled ITT population with an opportunity to reach Week 52)



BD = bronchodilator; BL = baseline; FEV_1 = forced expiratory volume in 1 second; ITT = intention-to-treat; LS = least squares; q2w = every two weeks; SE = standard error
Source: Sanofi 2023 [Data on file] Pooled analysis summary of clinical efficacy(174)

Other secondary endpoints

Change in pre-BD FEV_1 from baseline to Weeks 2, 4, 8, 24, 36 and 44

Improvements in pre-BD FEV_1 with dupilumab compared to placebo were observed at all timepoints assessed (Table 26).(179)

Table 26. Pooled analysis LS mean change from baseline in pre-BD FEV_1 up to Week 52 (pooled ITT population with an opportunity to reach Week 52)

	Dupilumab (n=830)	Placebo (n=830)
Change in pre-BD FEV_1 from baseline to Week 2[a]		
LS mean (SE), litre	0.133 (0.013)	0.070 (0.013)
LS mean difference vs. placebo (95% CI), litre	0.063 (0.034, 0.092); nominal p<0.0001	
Change in pre-BD FEV_1 from baseline to Week 4[a]		
LS mean (SE), litre	0.146 (0.014)	0.069 (0.014)
LS mean difference vs. placebo (95% CI), litre	0.077 (0.047, 0.107); nominal p<0.0001	
Change in pre-BD FEV_1 from baseline to Week 8[a]		
LS mean (SE), litre	0.138 (0.014)	0.065 (0.014)
LS mean difference vs. placebo (95% CI), litre; p-value	0.073 (0.043, 0.104); nominal p<0.0001	
Change in pre-BD FEV_1 from baseline to Week 12[a,b]		
LS mean (SE), litre	0.147 (0.013)	0.064 (0.013)
LS mean difference vs. placebo (95% CI), litre; p-value	0.083 (0.053, 0.112); nominal p<0.0001	
Change in pre-BD FEV_1 from baseline to Week 24[a]		
LS mean (SE), litre	0.062 (0.015)	0.159 (0.015)
LS mean difference vs. placebo (95% CI), litre; p-value	0.097 (0.064, 0.130); nominal p<0.0001	
Change in pre-BD FEV_1 from baseline to Week 36[a]		
LS mean (SE), litre	0.134 (0.015)	0.067 (0.015)
LS mean difference vs. placebo (95% CI), litre; p-value	0.067 (0.033, 0.101); nominal p=0.0001	
Change in pre-BD FEV_1 from baseline to Week 44[a]		
LS mean (SE), litre	0.075 (0.015)	0.163 (0.015)
Week 44 LS mean difference vs. placebo (95% CI), litre; p-value	0.088 (0.054, 0.121); nominal p<0.0001	
Change in pre-BD FEV_1 from baseline to Week 52[a,b]		
LS mean (SE), litre	0.133 (0.015)	0.059 (0.015)
LS mean difference vs. placebo (95% CI), litre; p-value	0.073 (0.040, 0.107); nominal p<0.0001	

BD = bronchodilator; CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; ITT = intention-to-treat; LS = least squares; MMRM = mixed-effect model with repeated measures; SE = standard error

[a] An MMRM model was used to derive the change per visit; Response variable: change from baseline in pre-BD FEV_1 up to Week 52; Covariates: treatment group, age, sex, height, region (pooled country), ICS dose, smoking status at screening, visit, treatment-by-visit interaction, baseline pre-bronchodilator FEV_1, and FEV_1 baseline-by-visit interaction.

[b] Key secondary endpoint

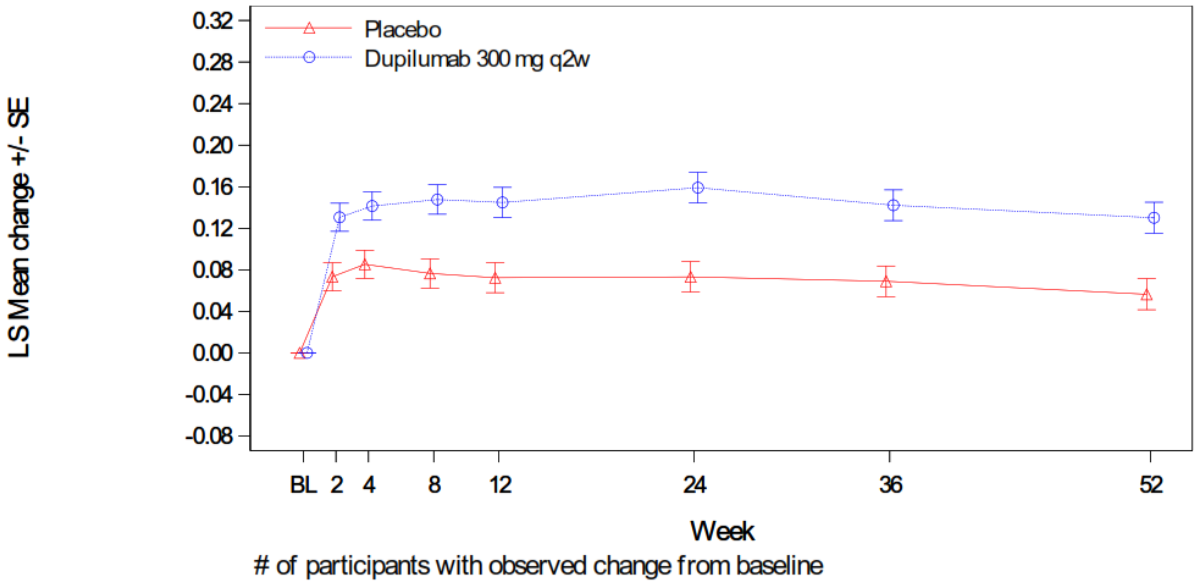
Source: Sanofi 2023 [Data on file] Pooled analysis summary of clinical efficacy appendix(179)

Change in post-BD FEV_1 from baseline to Weeks 2, 4, 8, 12, 24, 36 and 52

Consistent with the treatment effect observed for pre-BD FEV_1, dupilumab led to a rapid improvement in post-BD FEV_1 compared to placebo, as early as Week 2 (LS mean difference vs. placebo: +57 mL;

nominal p=0.001), which was maintained through to Week 52 (LS mean difference vs. placebo: +74 mL; nominal p<0.001; Figure 15).(174)

Figure 15. Pooled analysis LS mean change from baseline in post-BD FEV_1 up to Week 52 (pooled ITT population with an opportunity to reach Week 52)



# of participants with observed change from baseline

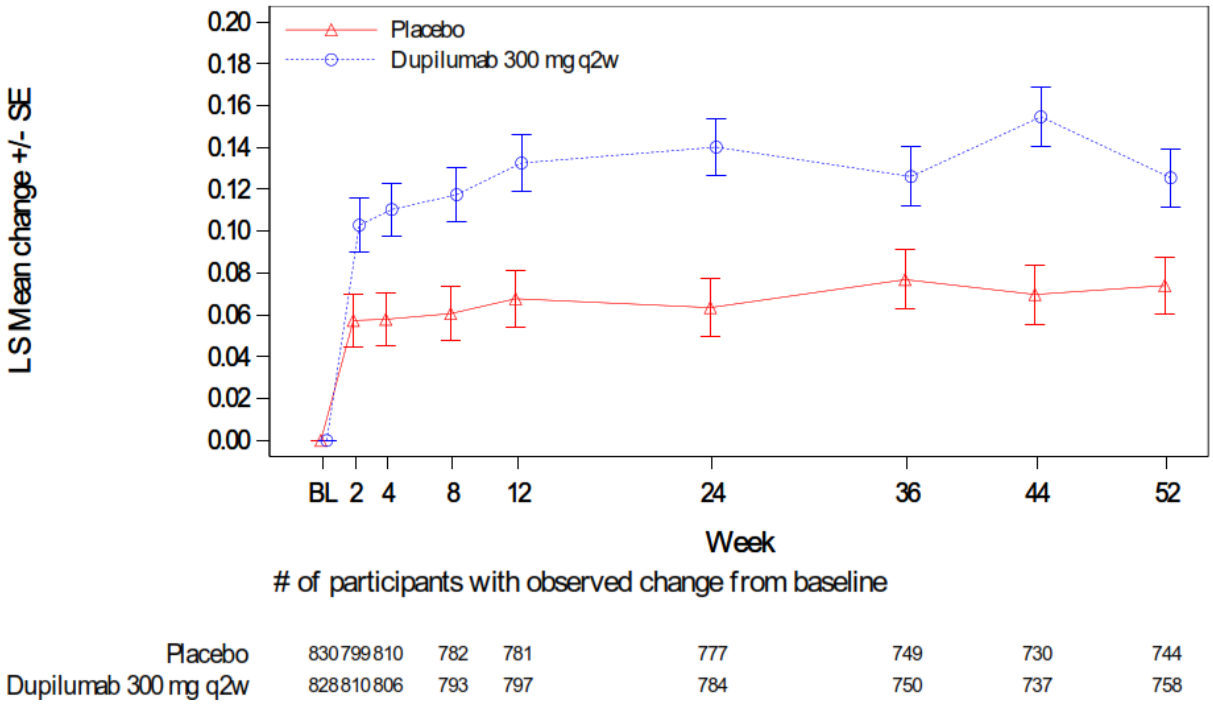
Placebo	830	798	808	780	767	750	748	738
Dupilumab 300 mg q2w	828	810	805	795	776	773	749	752

BD = bronchodilator; BL = baseline; FEV_1 = forced expiratory volume in 1 second; ITT = intention-to-treat; LS = least squares; q2w = every two weeks; SE = standard error
Source: Sanofi 2023 [Data on file] Pooled analysis summary of clinical efficacy appendix(179)

Change in pre-BD $FEF_{25-75\%}$ from baseline to Weeks 2, 4, 8, 12, 24, 36, 44 and 52

Dupilumab led to a rapid improvement in pre-BD $FEF_{25\%-75\%}$ as early as Week 2 (LS mean difference vs. placebo: +0.046 L/s; nominal p=0.0014), which was maintained throughout the treatment period (Week 52 LS mean difference vs. placebo: +0.051 L/s; nominal p=0.0012; Figure 16).(174)

Figure 16. Pooled analysis LS mean change from baseline in pre-BD $FEF_{25\%-75\%}$ (L/s) up to Week 52 (pooled ITT population with an opportunity to reach Week 52)



BD = bronchodilator; BL = baseline; FEF = forced expiratory flow; ITT = intention-to-treat; LS = least squares; q2w = every two weeks; SE = standard error
Source: Sanofi 2023 [Data on file] Pooled analysis summary of clinical efficacy(174)

Annualised rate of severe COPD exacerbations over the 52-week treatment period

The proportion of participants experiencing a severe COPD exacerbation over the 52-week treatment period was low in both the dupilumab and placebo arms (4.4% vs. 6.4%; rate ratio: 0.674; 95% CI: 0.438, 1.037; nominal p=0.0725; Table 27).(174, 179)

Table 27. Pooled analysis annualised rate of severe COPD exacerbations over the 52-week treatment period (pooled ITT population)

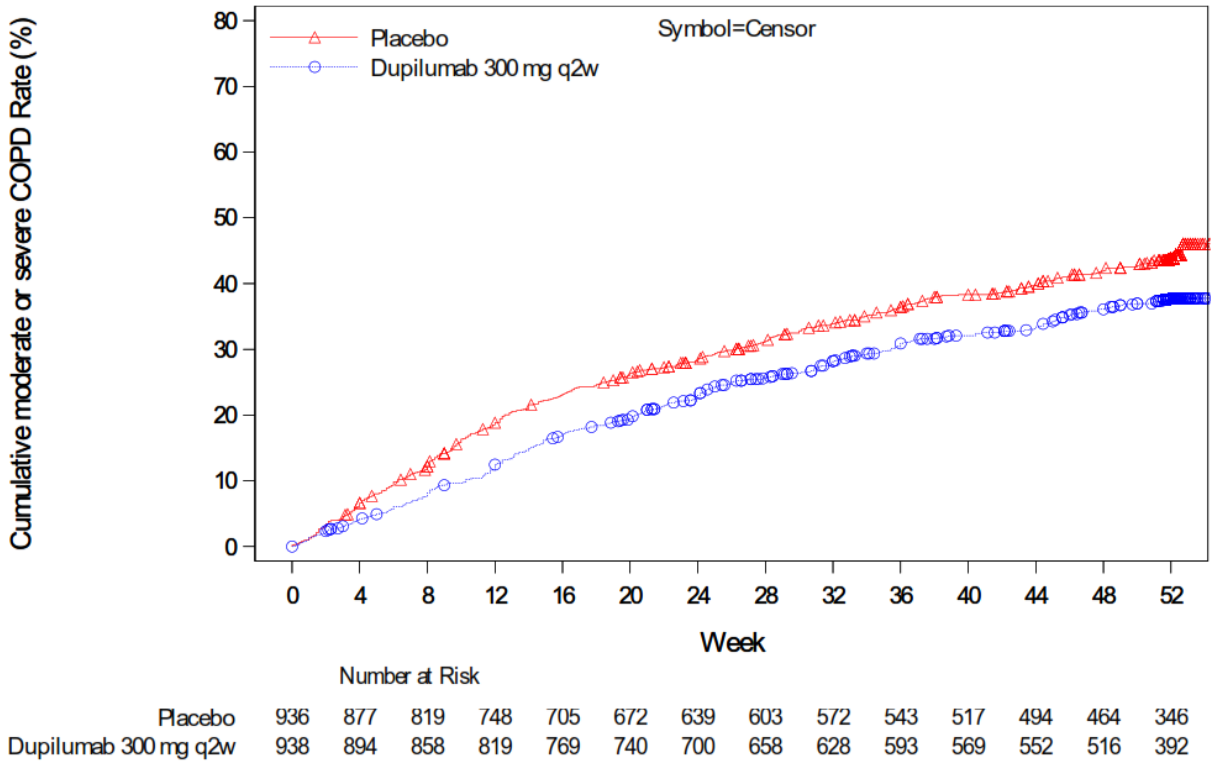
	Dupilumab (n=938)	Placebo (n=936)
Participants with ≥1 severe exacerbations, n (%)	41 (4.4)	60 (6.4)
Adjusted annualised severe exacerbation event rate[a]		
Estimate (95% CI)	0.084 (0.056, 0.125)	0.124 (0.085, 0.181)
Rate ratio vs. placebo (95% CI); p-value	0.674 (0.438, 1.037); nominal p=0.0725	

CI = confidence interval; COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroids; ITT = intention-to-treat
[a] A negative binomial model was used to derive the adjusted annualised rate. Response variable: total number of events occurring during the 52-week treatment period; covariates: treatment group, study, region (pooled country), ICS dose, smoking status at screening, baseline disease severity, and number of moderate or severe COPD exacerbation events ≤1 year prior to the study; offset variable: log-transformed treatment duration.
Source: Sanofi 2023 [Data on file] Pooled analysis summary of clinical efficacy;(174) Sanofi 2023 [Data on file] Pooled analysis summary of clinical efficacy appendix(179)

Time to first moderate or severe COPD exacerbation over the 52-week treatment period

Treatment with dupilumab delayed time to first moderate or severe COPD exacerbation compared to placebo (HR: 0.770; 95% CI: 0.666, 0.892; nominal p=0.0005), with the treatment effect observed as early as Week 4 (Figure 17).(174)

Figure 17. Pooled analysis Kaplan-Meier plot of time to first moderate or severe COPD exacerbation event during the 52-week treatment period (pooled ITT population)



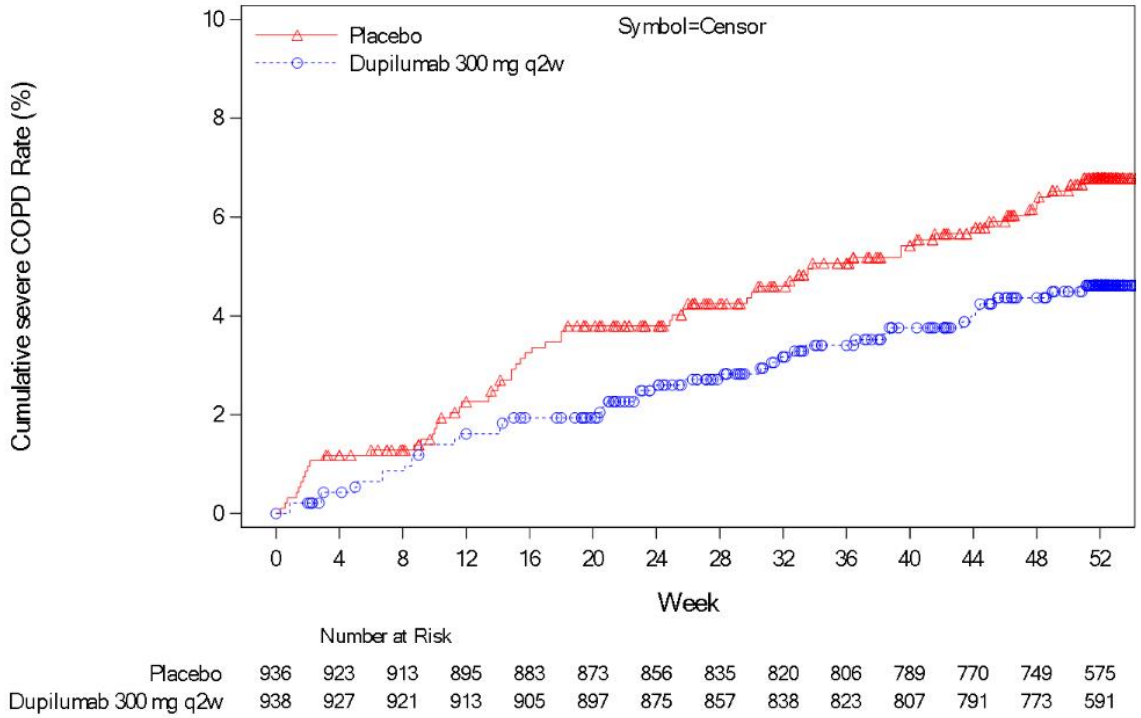
COPD = chronic obstructive pulmonary disease; ITT = intention-to-treat; q2w = every two weeks
Source: Sanofi 2023 [Data on file] Pooled analysis summary of clinical efficacy appendix(179)

Tertiary/exploratory endpoints

Time to first severe COPD exacerbation during the 52-week treatment period

Treatment with dupilumab delayed time to first severe COPD exacerbation compared to placebo, reducing the risk of first severe COPD exacerbation by 39% (HR: 0.611; 95% CI: 0.409, 0.912; nominal p=0.0160; Figure 18).(179)

Figure 18. Pooled analysis Kaplan-Meier plot of time to first severe COPD exacerbation event during the 52-week treatment period (pooled ITT population)



COPD = chronic obstructive pulmonary disease; ITT = intention-to-treat; q2w = every two weeks
Source: Sanofi 2023 [Data on file] Pooled analysis summary of clinical efficacy appendix(179)

Change in FVC from baseline to Weeks 12, 24 and 52

Dupilumab led to rapid improvements in pre-BD FVC and % predicted FVC compared to placebo as early as Week 2 (LS mean difference vs. placebo: +0.057 L; nominal p=0.0030 and +1.342%; nominal p=0.0098, respectively), which were maintained over the treatment period (Week 52 LS mean difference vs. placebo +0.075 L; nominal p=0.0010 and +1.925%; nominal p=0.0017).(179)

Similar rapid and sustained improvements were observed in post-BD FVC with dupilumab compared to placebo from Week 2 (LS mean difference vs. placebo: +0.048 L; nominal p=0.0096) over the treatment period (Week 52 LS mean difference vs. placebo: +0.071 L; nominal p=0.0014).(179)

Additional analyses

Systemic corticosteroid use over the 52-week treatment period

Systemic corticosteroids were used by 33.6% of participants receiving dupilumab and 39.1% of participants receiving placebo during the 52-week intervention period regardless of cause.(179) Dupilumab led to a 30% reduction in the annualised total number of systemic corticosteroid courses compared to placebo (relative risk: 0.701; 95% CI: 0.600, 0.819; nominal p<0.0001).(179) Furthermore, the unadjusted annualised total intake duration of systemic corticosteroids was lower with dupilumab compared to placebo (5.6 days vs 7.7 days).(179)

Antibiotic use over the 52-week treatment period

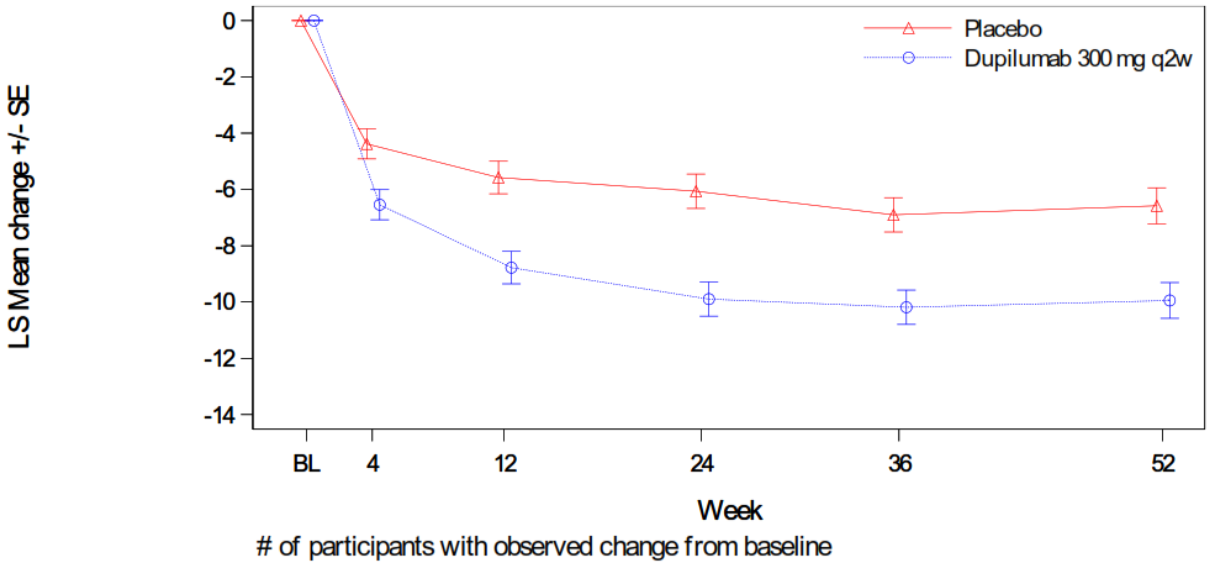
Antibiotics were used by 40.3% of participants receiving dupilumab and 44.3% of participants receiving placebo during the 52-week intervention period regardless of cause.(179) Dupilumab led to a 21% reduction in the annualised total number of antibiotic courses compared to placebo (relative risk: 0.791; 95% CI: 0.689, 0.907; nominal p=0.0008).(179) Furthermore, the unadjusted annualised total intake duration of antibiotics was lower with dupilumab compared to placebo (9.8 days vs 10.7 days).(179)

B.2.6.3.2. Patient-reported outcomes

Key secondary endpoint: Change from baseline in the SGRQ total score at Week 52

Dupilumab resulted in a greater reduction in SGRQ total score at Week 52 compared to placebo (LS mean difference: −3.4; 95% CI: −5.0; −1.8; nominal p<0.0001).(174) Improvements in HRQoL with dupilumab were reported as early as Week 4 (first measurement after baseline) and were sustained over the treatment period (Figure 19).(174)

Figure 19. Pooled analysis LS mean change from baseline in SGRQ total score up to Week 52 (pooled ITT population with an opportunity to reach Week 52)



# of participants with observed change from baseline

Placebo	808	764	748	720	732	710
Dupilumab 300 mg q2w	813	770	763	765	729	732

BL = baseline; ITT = intention-to-treat; LS = least squares; q2w = every two weeks; SE = standard error; SGRQ = St. George's Respiratory Questionnaire
Source: Sanofi 2023 [Data on file] Pooled analysis summary of clinical efficacy appendix(179)

Key secondary endpoint: Proportion of participants with an improvement in SGRQ score of ≥4 points (MCID) from baseline to Week 52

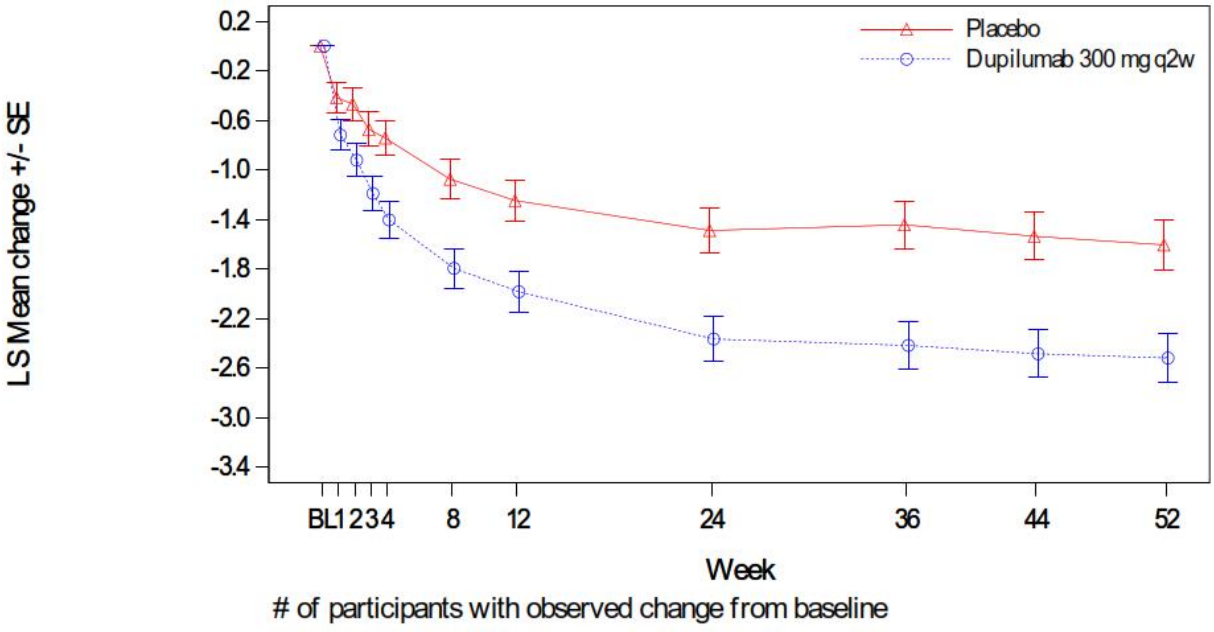
A higher proportion of participants in the dupilumab arm achieved a clinically meaningful improvement (reduction by ≥4 points) in SGRQ total score than in the placebo arm (51.4% vs. 44.6%; OR: 1.3; 95% CI: 1.1, 1.6; nominal p=0.0089).(174)

The SGRQ improvements observed with dupilumab are further strengthened by the positive correlation that has been reported between MCID improvements in FEV_1 and HRQoL data.(180)

Tertiary/exploratory endpoint: Change from baseline in E-RS: COPD total score at Week 52

Participants treated with dupilumab reported a greater reduction in E-RS: COPD total score at Week 52 compared to placebo (LS mean difference: −0.9; 95% CI: −1.4, −0.4; nominal p=0.0006).(174) Improvements in the severity of respiratory symptoms with dupilumab were observed as early as Week 1 (LS mean difference vs. placebo: −0.3; 95% CI: −0.6, 0.0; nominal p=0.0320) and were sustained over the treatment period (Week 52; Figure 20).(174)

Figure 20. Pooled analysis LS mean change from baseline in E-RS: COPD total score up to Week 52 (pooled ITT population with an opportunity to reach Week 52)



BL = baseline; E-RS: COPD = Evaluating Respiratory Symptoms in COPD; ITT = intention-to-treat; LS = least squares; q2w = every two weeks; SE = standard error
Source: Sanofi 2023 [Data on file] Pooled analysis summary of clinical efficacy(174)

B.2.7. Subgroup analysis

As described in Section B.2.3, the pre-planned and post-hoc subgroup analyses described in Table 28 were undertaken for BOREAS and NOTUS as well as the pooled analysis. COPD is a complex

disease, with heterogeneity in individual risk and clinical presentation (Section B.1.3.1). Subgroups were therefore selected to explore the impact of key demographic and disease characteristics.

Treatment by subgroup interaction and its p-value were derived by a negative binomial model for the annualised rate of moderate or severe COPD exacerbations at Week 52 (primary endpoint) and by a mixed-effect model with repeated measures (MMRM) model for change from baseline to Week 12 in the pre-BD FEV_1 (key secondary endpoint).(168, 169) More detailed information on the statistical analysis methods is provided in Section B.2.4.1.3.

Table 28. Comparative summary of trial subgroup methodology

Trial number (acronym)	BOREAS (NCT03930732)	NOTUS (NCT04456673)
Pre-planned subgroups	Demographics • Age group (<65 or ≥65 years; 40-64, 65-74, 75-80 years) • Gender (Male or Female) • Race (White or non-White) • Ethnicity (Hispanic/Latino or Not Hispanic/Latino) • Region • Territory • Baseline weight (<70, ≥70 to <90, ≥90 kg; <60, ≥60 kg) • Baseline BMI (<25, ≥25 to <30, ≥30 kg/m^2) Disease characteristics • ICS dose level at baseline (high, non-high, or none) • ICS dose at baseline (<median or ≥median) • Smoking status at screening (current or former smokers) • Number of moderate or severe COPD exacerbation events within one year prior to Visit 1 (≤2, 3, or ≥4)[a,b] • Number of severe COPD exacerbation events within one year prior to Visit 1 (0, 1, ≥2)[b] • Baseline predicted post-BD FEV_1% (<50% or ≥50%) • Baseline pre-BD FEV_1 (< or ≥ median) • Baseline FEV_1 reversibility (<12%, ≥12%; < or ≥ median) Biomarkers • Baseline FeNO (<20, ≥20 ppb) • Baseline eotaxin-3 (< or ≥ median) • Baseline IgE (< 100 , ≥100 IU/ml) • Baseline PARC (< or ≥ median) • Baseline fibrinogen (<350, ≥350 mg/dL)	Demographics • Age group (<65 or ≥65 years; 40-64, 65-74, 75-80 years) • Gender (Male or Female) • Race (White or non-White) • Ethnicity (Hispanic/Latino or not Hispanic/Latino) • Region • Territory • Baseline weight (<70, ≥70 to <90, ≥90 kg; <60, ≥60 kg) • Baseline BMI (<25, ≥25 to <30, ≥30 kg/m^2) Disease characteristics • ICS dose level at baseline (high, non-high, or none) • ICS dose at baseline (<median or ≥median) • Smoking status at screening (current or former smokers) • Number of moderate or severe COPD exacerbation events within one year prior to Visit 1 (≤2, 3, or ≥4)[a,b] • Number of severe COPD exacerbation events within one year prior to Visit 1 (0, 1, ≥2; 0, ≥1)[b] • Baseline predicted post-BD FEV_1% (<50% or ≥50%) • Baseline pre-BD FEV_1 (< or ≥ median) • Baseline FEV_1 reversibility (<12%, ≥12%; < or ≥ median) • Ongoing emphysema at baseline (yes or no)[c] • E-RS: COPD RS-Cough and Sputum (< or ≥ median) • Baseline BODE score (≤4 or >4) Biomarkers • Baseline FeNO (<20, ≥20 ppb) • Baseline eotaxin-3 (< or ≥ median)[d] • Baseline IgE (<100, ≥100 IU/ml) • Baseline PARC (< or ≥ median)[d]

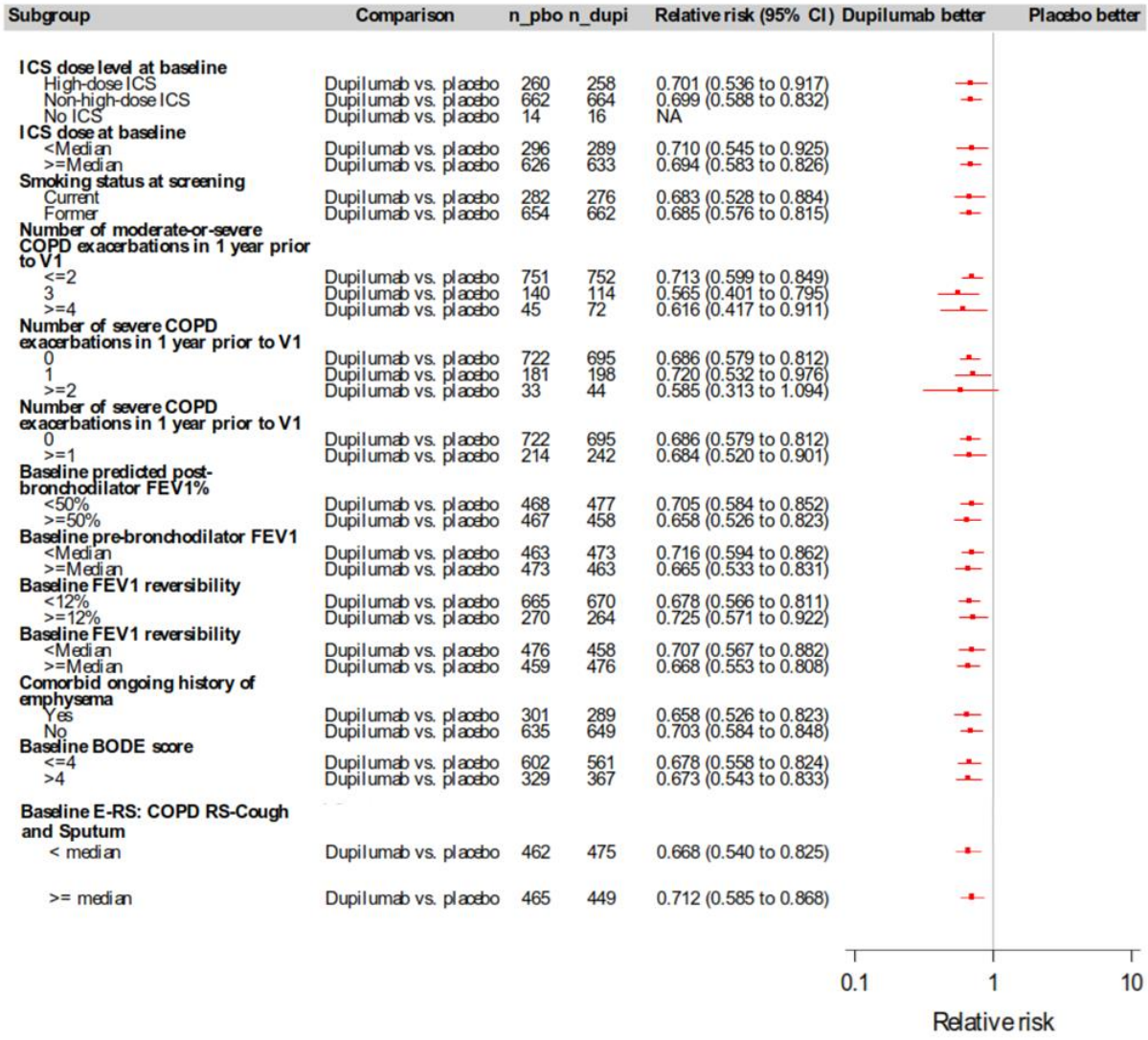
Trial number (acronym)	BOREAS (NCT03930732)	NOTUS (NCT04456673)
	• Maximum EOS counts during screening (≤0.3 to <0.5, ≥0.5 Giga/L)	• Baseline fibrinogen (<350, ≥350 mg/dL) • Maximum EOS counts during screening (<0.5, ≥0.5 Giga/L)
Post-hoc subgroups	• Ongoing emphysema at baseline (yes, no)[c] • E-RS: COPD RS-Cough and Sputum (< or ≥ median) • Baseline BODE index score (low, high) • Number of severe COPD exacerbation events within one year prior to Visit 1 (0, ≥1; primary endpoint only)[b]	None

[a] Moderate exacerbations included those requiring systemic glucocorticoid treatment and/or antibiotic treatment. Two events were considered separate if occurred ≥14 days apart.
[b] Severe exacerbations included those requiring hospitalisation or emergency department observation >24 hours. Two events were considered separate if occurred ≥14 days apart.
[c] Investigator reported active condition at baseline.
[d] Analyses of baseline plasma eotaxin-3 and serum PARC were not performed at the time of the NOTUS interim analysis data cut-off date.
BMI = body mass index; BODE = body mass index, airflow obstruction, dyspnoea, and exercise; COPD = chronic obstructive pulmonary disease; EOS = eosinophil; E-RS: COPD = Evaluating Respiratory Symptoms in COPD; FeNO = fractional exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; IgE = immunoglobulin E; MRC = Medical Research Council; SC = subcutaneous; PARC = pulmonary and activation-regulated chemokine; pre-BD = pre-bronchodilator
Source: Bhatt et al. 2023(168); Bhatt et al. 2024(169)

All analysed disease characteristic and biomarker subgroups exhibited a statistically significant reduction in the rate of moderate or severe exacerbations, with the exception of the subgroup with two or more prior severe exacerbations.(174) The treatment effect in patients with two or more prior severe exacerbations was directionally greater than all but one subgroup, but comprised a low number of patients which contributed to a wide confidence interval.(174) Nearly all subgroups exhibited an increase in FEV_1 in favour of dupilumab versus placebo.(174) These results are consistent with the primary and secondary endpoints in the ITT population, and suggest a broad efficacy of dupilumab across different patient characteristics of those recruited.

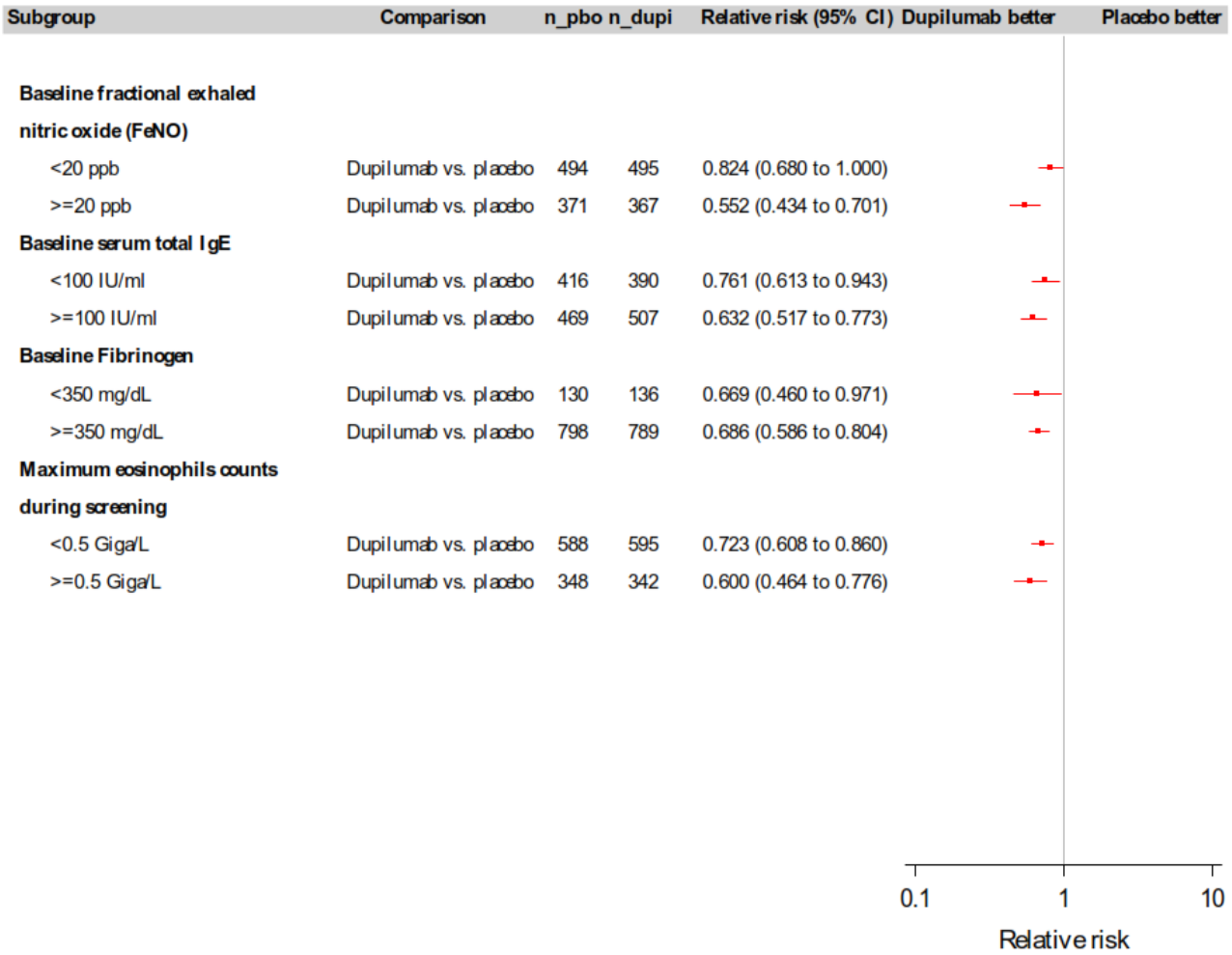
Results from the pooled analysis of the annualised rate of moderate or severe COPD exacerbations by disease characteristics and biomarker subgroups are presented in Figure 21 and Figure 22, respectively.(174) The results of all subgroup analyses are provided in Appendix E.

Figure 21. Pooled analysis annualised rate of moderate or severe COPD exacerbations forest plot of relative risk by disease characteristics subgroups (pooled ITT population)



BODE = body mass index, airflow obstruction, dyspnoea and exercise capacity; CI = confidence interval; COPD = chronic obstructive pulmonary disease; dupi = dupilumab; E-RS: COPD = Evaluating Respiratory Symptoms in COPD; ICS = inhaled corticosteroids; ITT = intention-to-treat; FEV_1 = forced expiratory volume in 1 second; NA = not analysable; pbo = placebo; V1 = Visit 1
Source: Sanofi 2023 [Data on file] Pooled analysis summary of clinical efficacy(174)

Figure 22. Pooled analysis annualised rate of moderate or severe COPD exacerbations forest plot of relative risk by biomarker subgroups (pooled ITT population)



CI = confidence interval; COPD = chronic obstructive pulmonary disease; dupi = dupilumab; IgE = immunoglobulin E; ITT = intention-to-treat; pbo = placebo; ppb = parts per billion
Source: Sanofi 2023 [Data on file] Pooled analysis summary of clinical efficacy(174)

B.2.8. Meta-analysis

Beyond the BOREAS and NOTUS trials, no other data are available to assess the clinical effectiveness of dupilumab as add-on maintenance treatment for adults with uncontrolled COPD (≥2 moderate or ≥1 severe historical exacerbations within 12 months) and Type 2 inflammation (blood EOS ≥300 cells/μL) whilst on triple therapy (double therapy if ICS is not appropriate). As a result, no meta-analysis was conducted.

B.2.9. Indirect and mixed treatment comparisons

B.2.9.1. Exploratory analysis based on Martinez 2018.

An SLR of clinical evidence conducted in August 2024 did not identify any RCTs studying the efficacy of roflumilast in patients with blood EOS ≥300 cells/μl at baseline. The only identified source of data in the raised blood EOS population was a pooled post-hoc analysis(140) of the REACT(136) and

RE2SPOND(137) trials. Due to a number of substantial differences between the REACT and RE2SPOND trials compared with BOREAS and NOTUS, including differences in the background therapies used (only 42% of patients in REACT and RE2SPOND were on triple therapy compared with over 98% in BOREAS and NOTUS) and disease severity (REACT and RE2SPOND included only severe/very COPD patients while BOREAS and NOTUS included moderate/severe), an ITC was not recommended (Appendix D).

However, despite this recommendation, an exploratory ITC has been undertaken to address the inclusion of roflumilast in the final NICE scope. It is important to note that these exploratory analyses are extremely limited, and the results presented are not considered to be robust. Therefore, meaningful conclusions on the comparative efficacy and safety of dupilumab and roflumilast cannot be drawn from this exploratory ITC.

In order to make comparisons possible, the pooled BOREAS and NOTUS cohort was restricted to a 'REACT-like' population, defined as:

- FEV_1 (post-bronchodilator) ≤50% of predicted,
- Former smokers (defined as smoking cessation at least one year ago) or current smokers both with a smoking history of at least 20 pack years,
- At least two documented moderate or severe COPD exacerbations within one year prior to baseline visit.

These restrictions do not address the remaining underlying mismatch of background therapies, the differences in the severity of COPD in the trial populations, or the nature of underlying inflammation (Type 2 vs all), but allowed for the following Bucher's ITC analyses to be attempted for efficacy:

- Annualised rate of moderate or severe COPD exacerbation (rate ratio)
- Annualised rate of severe COPD exacerbation (rate ratio)
- Annualised rate of moderate COPD exacerbation (rate ratio).

The list of efficacy endpoints analysed in the ITC is limited by data availability for roflumilast, as results for the raised blood EOS population were not reported for any other efficacy endpoints.

Additionally, Bucher's ITC analyses were conducted for the following safety endpoints:

- Proportion of patients with ≥1 TEAE / AE (odds ratio)
- Proportion of patients with ≥1 serious TEAEs / SAE (odds ratio)
- Treatment discontinuation (odds ratio).

Analyses were conducted using the overall population from the REACT and RE2SPOND trials.

Results of the exploratory ITC analyses are presented in Table 29. As outlined above, given the substantial limitations of the Bucher's ITC, the results are not considered robust and should not be used to draw conclusions about the relative efficacy and safety of dupilumab versus roflumilast.

Table 29. Results of the exploratory ITC of dupilumab versus roflumilast

Endpoint	Bucher's ITC Dupilumab 300 mg vs. Roflumilast 500 µg
Efficacy endpoints; rate ratio [95% CI]	
Annualised rate of moderate or severe COPD exacerbation	[redacted]
Annualised rate of severe COPD exacerbations	[redacted]
Annualised rate of moderate COPD exacerbations	[redacted]
Safety endpoints; odds ratio [95% CI]:	
Proportion of patients with ≥1 TEAE	[redacted]
Proportion of patients with ≥ 1 SAE	[redacted]
Proportion of patients with treatment discontinuation	[redacted]

CI = confidence interval; COPD = chronic obstructive pulmonary disease; ITC = indirect treatment comparison
* Considered as statistically significant in favour of dupilumab (at significance level of 0.05, with no multiple testing adjustment)

B.2.9.2. Alternative approach to explore the impact of background therapy on roflumilast efficacy

The annualised rate ratio of severe and moderate exacerbations in the pooled REACT and RE2SPOND studies for roflumilast with raised blood EOS compared to the placebo is reported as 0.77 (95% CI: 0.61, 0.97) in Martinez et al. 2018(140) but because the REACT and RE2SPOND studies for roflumilast were conducted before the superiority of triple therapy was established, this is the aggregate of the treatment effect of roflumilast on top of a mixture of double and triple therapy. We have noted earlier that the dupilumab trials BOREAS and NOTUS for patients with uncontrolled COPD (≥2 moderate or ≥1 severe historical exacerbations within 12 months) with Type 2 inflammation (blood EOS ≥300 cells/µL) were conducted more recently and are almost exclusively on a background of triple therapy but there is no published evidence for the treatment effect of roflumilast in the raised blood EOS population on top of triple therapy alone. Therefore, the treatment comparison above may be biased by this. Hence, we have made best efforts to estimate the likely effect size of roflumilast as add-on to triple therapy. This is described in brief below and in detail in Appendix T.

A starting point to estimate the efficacy of roflumilast on top of each background therapy is to consider the efficacy of triple therapy versus double therapy alone. To do this, a targeted literature review was conducted to identify and synthesise the expected treatment effect observed between double and triple therapy. (See Appendix T). The results are then used to adjust the roflumilast treatment effect based on background therapy and finally to conduct a pairwise Bucher's ITC.

Seven double-blind RCTs were identified, six of which provided annualised rates for moderate or severe exacerbation outcomes to evaluate the relative efficacy of triple therapy versus double therapy. The group of studies most closely aligned with the requirements of this analysis provided data on the 'high eosinophilic and severe COPD' group, but two further groups were identified for sensitivity analysis: 'high eosinophilic' and 'severe COPD'.

These trials were combined using a direct meta-analysis method.(181) The relative efficacy was estimated using random effects models based on the log annualised rate ratio. Heterogeneity was assessed using the I^2 statistic and the χ^2 test. Missing standard error values were replaced with the highest standard error observed among the included estimates. (See Appendix T).

Overall, the relative effect of the annualised rate of severe or moderate exacerbation comparing triple therapy versus double therapy is 0.84 (95% CI: 0.81; 0.88). For the high eosinophilic and severe COPD group, the annualised rate is 0.80 (95% CI: 0.47; 1.36).

Two options to estimate the roflumilast treatment effect on triple background therapy informed by the meta-analysis above were examined. The methodology and full results are provided in Appendix T.

- The '*Direct'* scenario: Assumes that the treatment effect of roflumilast on top of double therapy is equivalent to the treatment effect of triple therapy versus double therapy.
    - The results for this scenario in the 'high eosinophilic and severe COPD' group were 0.75 (95% CI: 0.59; 0.94) for triple therapy background and 0.80 (95% CI: 0.63; 1.01) for double therapy background.
- The *'By ratio'* scenario: Adjustment of the roflumilast treatment effect based on the ratio observed between double and triple therapy. This assumes that a proportion of the gain in treatment efficacy of roflumilast comes from increasing two treatments to three.
    - The results for this scenario in the 'high eosinophilic and severe COPD' group were 0.85 (95% CI: 0.67; 1.07) for triple therapy background and 0.68 (95% CI: 0.54; 0.85) for double therapy background.

The direct adjustment scenario is likely to overestimate the roflumilast treatment effect on top of triple background therapy because it assumes that roflumilast on top of double therapy is equivalent to the treatment effect of triple therapy alone. It is highly unlikely that roflumilast efficacy would be higher on top of triple therapy than double therapy from a clinical perspective (rate ratio on top of double therapy: 0.80 [95% CI: 0.63, 1.01] vs rate ratio on top of triple therapy: 0.75 [95% CI: 0.59, 0.94]) and contradicts the GOLD global strategy to add-on top of triple therapy. The scenario 'by ratio' is more credible but may overestimate the roflumilast effect on top of double therapy and therefore reduce the treatment effect on top of triple therapy. The treatment effect on top of triple therapy is 0.85 (95% CI: 0.67; 1.07) in this scenario which whilst directionally better does not reach significance. Clearly these analyses are highly exploratory and should be treated with caution, but do highlight significant uncertainty in providing a robust estimate for the treatment effect of roflumilast on top of triple therapy in the raised blood EOS population.

We have carried out a naïve pairwise Bucher's ITC to compare the pooled REACT and RE2SPOND studies adjusted to reflect raised blood EOS on a background of triple therapy with the pooled BOREAS and NOTUS data. The results are shown in Table 30.

Table 30. Pairwise Bucher's ITC (raised blood EOS, triple background therapy), annualised rate ratio

Study	Treatment	N	Annualised rate of moderate or severe COPD exacerbation [95% CI]	Rate ratio [95% CI]	Rate ratio pooled estimate [95% CI]	Bucher's ITC Dupilumab 300 mg vs. Roflumilast 500 µg
BOREAS	Dupilumab 300 mg	468	0.78 [0.64; 0.93]	0.70 [0.58; 0.86]	0.68 [0.59; 0.79]	[redacted]
	Placebo	471	1.10 [0.93; 1.3]			
NOTUS	Dupilumab 300 mg	470	0.859 [0.699; 1.057]	0.66 [0.54; 0.82]		
	Placebo	465	1.295 [1.048; 1.6]			
'By Ratio' method: REACT & RE2SPOND (pooled, raised EOS, triple therapy)	Roflumilast 500 µg	NA	NA	0.85 [0.67; 1.07]	-	
	Placebo	NA	NA			
'Direct' method: REACT & RE2SPOND (pooled, raised EOS, triple therapy)	Roflumilast 500 µg	NA	NA	0.75 [0.59; 0.94]	-	[redacted]
	Placebo	NA	NA			

CI = confidence interval; EOS = eosinophils; ITC = indirect treatment comparison; NA = not applicable

The naïve Bucher's ITC shows that, whilst not statistically significant, there is a signal suggesting the treatment effect of dupilumab vs roflumilast in the raised blood EOS population on top of triple therapy is directionally superior. These results are tested in sensitivity analysis for the exploratory comparison vs roflumilast in Section B.3.11.4.

B.2.10. Adverse reactions

The safety profile of dupilumab has been established through an extensive clinical development programme involving 15,834 participants (as of 28 March 2024) included in the safety population and 12,250 exposed to dupilumab of various ages and in multiple indications (atopic dermatitis, asthma, rhinosinusitis, eosinophilic oesophagitis, allergy, COPD, prurigo nodularis, urticaria, bullous pemphigoid, allergic bronchopulmonary aspergillosis, chronic pruritus of unknown origin, ulcerative colitis and eosinophilic gastritis.(182) The cumulative exposure to dupilumab parenteral formulations is estimated to be 1.9 million patient years(182) and to date over 1 million patients have been treated with dupilumab for licenced indications worldwide.(183, 184) Favourable long-term safety and tolerability of dupilumab have been demonstrated based on 5-year safety data, contributing to a well-characterised benefit-risk profile.(185) Furthermore according to the latest Periodic Benefit-Risk Evaluation Report based on the evaluation of the cumulative safety data and the benefit-risk analysis, the benefit-risk balance of dupilumab across all indications remains positive in the currently approved conditions of use.(182)

In the BOREAS and NOTUS trials, dupilumab demonstrated a favourable safety and tolerability profile in adults with uncontrolled COPD and evidence of Type 2 inflammation on triple therapy (LABA + LAMA + ICS; or LABA + LAMA if ICS was not appropriate).(168, 169) A detailed summary of the safety profile in each trial as well as the pooled analysis is provided in the following sections. Additionally, to ensure all relevant safety evidence for dupilumab and potential comparator therapies was identified, systematic searches for RCT safety outcomes were carried out as part of the clinical SLR. Results are presented in Appendix F.

B.2.10.1. Pooled analysis of BOREAS and NOTUS

The safety data presented in this section and subsequently used in the cost-effectiveness modelling are based on the pooled analysis of BOREAS and NOTUS, including a total of 1,872 participants who were randomised and exposed to the study intervention (938 in the dupilumab arm and 934 in the placebo arm).(177)

An overview of the safety profiles of dupilumab and placebo in the pooled analysis is presented in Table 31. Overall, a similar frequency of any TEAE was reported among participants in the dupilumab and placebo arms (72.1% and 71.0%, respectively), with a comparable proportion of participants permanently discontinuing the study due to TEAEs in both treatment arms (3.4% vs. 3.0%).(177) Overall, 125 (13.3%) participants in the dupilumab arm and 147 (15.7%) participants in the placebo arm reported treatment emergent SAEs.(177) A total of 34 patients had TEAEs leading to death (19 in the dupilumab arm and 15 in the placebo arm), none of which were attributed to treatment by the investigator.(177)

Table 31. Pooled analysis overview of safety profile (pooled safety population; up to Week 52)

	Dupilumab (n=938)	Placebo (n=934)
Participants with any TEAE, n (%)	676 (72.1)	663 (71.0)
Participants with any severe TEAE, n (%)	108 (11.5)	117 (12.5)
Participants with any treatment emergent SAE, n (%)	125 (13.3)	147 (15.7)
Participants with any TEAE leading to death, n (%)	19 (2.0)	15 (1.6)
Participants with any TEAE leading to permanent study intervention discontinuation, n (%)	32 (3.4)	28 (3.0)
Participants with any treatment emergent AESI[a], n (%)	79 (8.4)	76 (8.1)
Participants with any TEAE related to IMP, n (%)	50 (5.3)	36 (3.9)

AESI = adverse event of special interest; ALT = alanine aminotransferase; IMP = investigational medicinal product; NIMP = non-investigational medicinal product; SAE = serious adverse event; TEAE = treatment emergent adverse event
[a] AESIs included systematic hypersensitivity, severe injection site reactions (lasting >24 hours), infections (i.e., serious infections, parasitic or opportunistic infections, infection requiring parenteral antimicrobial therapy or oral antimicrobial therapy for >2 weeks), pregnancy, symptomatic overdose with IMP or NIMP, clinically symptomatic eosinophilia, severe conjunctivitis or blepharitis, keratitis and significant ALT elevation.
Source: Sanofi 2023 [Data on file] Pooled analysis summary of clinical safety(177)

The most common TEAEs in the dupilumab group compared to the placebo group (≥2% in the dupilumab group and a difference of ≥1% vs. the placebo group) were headache (7.8% vs. 6.6%), back pain (4.5% vs. 3.1%), urinary tract infection (3.0% vs. 1.9%) and gastritis (2.0% vs. 0.7%) (Table 32).(177) The most common TEAEs in the placebo group compared to the dupilumab group (≥2% in

the placebo group and a difference of ≥1% vs. the dupilumab group) were COPD (6.9% vs. 5.3%) and hypertension (4.6% vs. 3.4%).(177)

A reduced incidence of AEs commonly associated with COPD (respiratory, cardiac and vascular events) was reported with dupilumab compared to placebo:(177)

- AEs in the 'respiratory, thoracic and mediastinal disorders' system organ class occurred in 13.1% of participants in the dupilumab arm and 14.2% of participants in the placebo arm
- AEs in the 'cardiac disorders' system organ class occurred in 6.0% of participants in the dupilumab arm and 6.6% of participants in the placebo arm
    - The incidence of MACE was lower in the dupilumab arm compared with the placebo arm, including cardiovascular-related mortality (Table 32)
- AEs in the 'vascular disorders' system organ class occurred in 5.8% of participants in the dupilumab arm and 7.8% of participants in the placebo arm

Participants in the dupilumab and placebo groups experienced a similar frequency of TEAEs associated with COVID-19 (including COVID-19, COVID-19 pneumonia, suspected COVID-19 and SARS-CoV-2 test positive; 9.0% v. 8.8%, respectively).(177) The investigator did not consider the TEAEs associated with COVID-19 to be related to dupilumab.(177)

Table 32. Pooled analysis summary of TEAEs occurring in ≥2% of participants by system organ class and major adverse cardiovascular events up to Week 52 (pooled safety population)

System Organ Class Preferred term, n (%)	Dupilumab (n=938)	Placebo (n=934)
Any class	676 (72.1)	663 (71.0)
Infections and infestations	402 (42.9)	406 (43.5)
Nasopharyngitis	**73 (7.8)**	**69 (7.4)**
COVID-19	**65 (6.9)**	**66 (7.1)**
Upper respiratory tract infection	**50 (5.3)**	**57 (6.1)**
Bronchitis	37 (3.9)	42 (4.5)
Urinary tract infection	28 (3.0)	18 (1.9)
Rhinitis	24 (2.6)	17 (1.8)
Pneumonia	21 (2.2)	25 (2.7)
Lower respiratory tract infection	13 (1.4)	21 (2.2)
Nervous system disorders	108 (11.5)	108 (11.6)
Headache	**73 (7.8)**	**62 (6.6)**
Vascular disorders	54 (5.8)	73 (7.8)
Hypertension	32 (3.4)	43 (4.6)
Respiratory, thoracic and mediastinal disorders	123 (13.1)	133 (14.2)
Chronic obstructive pulmonary disease	**50 (5.3)**	**64 (6.9)**
Gastrointestinal disorders	135 (14.4)	130 (13.9)
Diarrhoea	35 (3.7)	28 (3.0)
Toothache	20 (2.1)	11 (1.2)

System Organ Class Preferred term, n (%)	Dupilumab (n=938)	Placebo (n=934)
Gastritis	19 (2.0)	7 (0.7)
Musculoskeletal and connective tissue disorders	126 (13.4)	121 (13.0)
Back pain	42 (4.5)	29 (3.1)
Arthralgia	29 (3.1)	25 (2.7)
Injury, poisoning and procedural complications	122 (13.0)	139 (14.9)
Accidental overdose	**57 (6.1)**	**62 (6.6)**
Fall	12 (1.3)	19 (2.0)
Cardiac disorders	**56 (6.0)**	**62 (6.6)**
Cardiac arrhythmias	29 (3.1)	35 (3.7)
Cardiac disorders, signs and symptoms NEC	2 (0.2)	5 (0.5)
Cardiac valve disorders	5 (0.5)	2 (0.2)
Coronary artery disorders	10 (1.1)	16 (1.7)
Heart failures	15 (1.6)	14 (1.5)
Myocardial disorders	1 (0.1)	1 (0.1)
Pericardial disorders	2 (0.2)	0
Major adverse cardiovascular events (adjudicated)	7 (0.7)	16 (1.7)
Non-fatal stroke	4 (0.4)	5 (0.5)
Cardiovascular deaths	2 (0.2)	4 (0.4)
Non-fatal myocardial infarction	1 (0.1)	7 (0.7)

COVID-19 = coronavirus disease 2019; NEC = not elsewhere classified; TEAE = treatment emergent adverse event
Note: Bold font indicates the most common TEAEs (≥5% in either treatment arm) by preferred term.
Source: Sanofi 2023 [Data on file] Pooled analysis summary of clinical safety(177)

B.2.11. Ongoing studies

As of October 2024, there are no ongoing Sanofi-led studies for dupilumab in COPD.

B.2.12. Interpretation of clinical effectiveness and safety evidence

Summary and interpretation of the evidence

COPD is a debilitating disease associated with a high clinical, humanistic and economic burden (Section B.1.3). Despite maximal treatment with triple inhaled therapy, almost two-thirds of patients continue to experience moderate or severe exacerbations.(26, 40) Exacerbations are unpleasant and disruptive to patients, can result in patient hospitalisation and consume significant NHS resource, and have long-lasting effects including an increased risk of future and more frequent exacerbations, CV events and irreversible lung damage.(27-30, 92, 123)

The burden of uncontrolled COPD is particularly high in patients with Type 2 inflammation, who have an increased risk of exacerbations and accelerated lung function decline.(41, 42) Currently recommended treatment options in England for patients who continue to experience exacerbations despite triple therapy (or double therapy if ICS is not appropriate) are non-targeted (4, 7, 8, 136, 137, 142, 144, 145) There is therefore an unmet need for a targeted, effective and well-tolerated treatment

that can provide significant clinical improvements in terms of exacerbation reduction, lung function, HRQoL and symptoms in patients with uncontrolled COPD despite triple therapy, particularly those with Type 2 inflammation who experience a higher burden and worse prognosis.

Dupilumab is a recombinant human IgG4 monoclonal antibody that inhibits IL-4 and IL-13 signalling and is intended as add-on maintenance treatment for adult patients with uncontrolled COPD (≥2 moderate or ≥1 severe historical exacerbations within 12 months) with Type 2 inflammation (blood EOS ≥300 cells/μL) on triple therapy or double therapy if ICS is not appropriate.(185) Data used to support the efficacy and safety of dupilumab in COPD for this submission were taken directly from the replicate phase III BOREAS and NOTUS RCTs, which represent the best available evidence to address the decision problem.(168, 169) Results from BOREAS and NOTUS were pooled as part of a prespecified protocol to increase the statistical power of the efficacy and safety analyses; this approach was appropriate due to the almost identical design of the studies and because there were no significant differences in study outcomes between the studies.(174, 177)

Results from both the pooled analysis and the individual phase III trials demonstrate the efficacy, safety and tolerability of dupilumab versus placebo in patients with uncontrolled COPD (≥2 moderate or ≥1 severe historical exacerbations within 12 months) with Type 2 inflammation (blood EOS ≥300 cells/μL), when used as add-on to triple therapy (or double therapy if ICS is not appropriate).(168, 169, 174, 177) Based on the pooled analysis:(174)

- Dupilumab resulted in a clinically meaningful 31% reduction in the annualised rate of moderate or severe exacerbations compared to placebo (rate ratio: 0.69; 95% CI: 0.60, 0.79; nominal p<0.0001), with improvements observed as early as Week 4 and progressively increasing up to Week 52.
- Improvements in pre-BD FEV_1 were greater with dupilumab over placebo at Week 12 (147 ml vs. 64 ml; LS mean difference: +83 ml; 95% CI: 53, 112; nominal p<0.0001) and were maintained through Week 52 (133 ml vs. 59 ml; LS mean difference: +73 ml; 95% CI: 40, 107; nominal p<0.0001). Similarly, dupilumab led to rapid and sustained improvements in post-BD FEV_1, pre-BD $FEF_{25-75\%}$ and pre-BD FVC compared to placebo.
- Dupilumab resulted in a greater reduction in SGRQ total score at Week 52 compared to placebo (LS mean difference: −3.4; 95% CI: −5.0; −1.8; nominal p<0.0001), indicating improved HRQoL. A higher proportion of participants in the dupilumab arm achieved a clinically meaningful improvement in SGRQ total score than in the placebo arm (51.4% vs. 44.6%; OR: 1.3; 95% CI: 1.1, 1.6; nominal p=0.0089).
- Participants treated with dupilumab reported a greater reduction in E-RS: COPD total score at Week 52 compared to placebo (LS mean difference: −0.9; 95% CI: −1.4, −0.4; nominal p=0.0006), indicating an improvement in the severity of respiratory symptoms with dupilumab.

In the BOREAS and NOTUS trials, dupilumab demonstrated a favourable safety and tolerability profile in adults with uncontrolled COPD (≥2 moderate or ≥1 severe historical exacerbations within 12 months) with Type 2 inflammation (blood EOS ≥300 cells/μL) on triple therapy (LABA + LAMA + ICS; or LABA + LAMA if ICS is not appropriate).(168, 169) Overall, a similar frequency of any TEAE was reported among participants in the dupilumab and placebo arms (72.1% and 71.0%, respectively).(177) The proportion of participants permanently discontinuing the study due to TEAEs was comparable in both treatment arms (3.4% vs. 3.0%).(177) A total of 19 participant receiving dupilumab and 15 patients receiving placebo had TEAEs leading to death; none were attributed to treatment by the investigator.(177) A similar or reduced incidence of AEs commonly associated with COPD (respiratory, cardiac and vascular events) was reported with dupilumab compared to placebo in both trials.(177)

Dupilumab is supported by a robust data package from two randomised, placebo-controlled, double-blind, 52-week phase III trials and is the first biologic in COPD to demonstrate statistically significant clinical improvements in exacerbations, lung function, HRQoL and symptoms that are sustained across 52 weeks. The consistency of outcome results between the two trials, and in the combined analysis, are confirmatory of the efficacy observed. Additionally, positive outcomes across multiple domains; exacerbation risk, lung function, symptoms and quality of life, are indicative of a treatment that effectively targets the underlying drivers of disease in these patients (Type 2 inflammation). Dupilumab is an add-on treatment to maximal inhaled therapy and therefore the benefits observed in COPD outcomes in the BOREAS and NOTUS trials should be considered in addition to the demonstrated benefits of inhaled therapies.(168, 169) Dupilumab has an established robust safety profile, validated by clinical trials and further supported by real-world safety data across multiple indications, with no new safety signals identified in patients with COPD.(182) Dupilumab has the potential to generate a significant step-change in the effective treatment of uncontrolled COPD with Type 2 inflammation, providing meaningful benefits to a burdened patient population with no other treatment options.

Dupilumab is currently reimbursed in Germany and on 24 September 2024 the German public radio and television broadcaster, Norddeutscher Rundfunk (NDR), released a video (not commissioned by Sanofi/Regeneron), which included the experience of a COPD patient on treatment with dupilumab.(186) The patient explained that:

> ***"After 4 days, I recognised an improvement. I could again dress up in the morning, I could take a shower, I could walk again, which was an experience I haven't had in the last year. It's amazing, simply amazing."*** *(Translated from German COPD patient testimonial on his experience with dupilumab)*

B.2.12.2. Key uncertainties and/or evidence gaps

- **The patient populations enrolled in the BOREAS and NOTUS trials are predominantly from outside of England**

Overall, one third of the BOREAS trial sites and almost half of the NOTUS sites were in the EU, with 39.1% of patients in the pooled ITT analysis enrolled from the EU.(168, 169, 174) BOREAS did not include sites in England, while the NOTUS trial enrolled 12 patients from 11 sites in England.(169)

Data from both BOREAS and NOTUS are expected to be applicable to patients in routine clinical practice in England. The majority of patients (98.2%) in BOREAS and NOTUS received triple background therapy,(174) consistent with the NICE 2019 guidelines which recommend escalation to triple inhaled therapies for patients with COPD who continue to experience limiting symptoms and exacerbations despite all other pharmacological and non-pharmacological interventions.(7) In an advisory board conducted by Sanofi in July 2024, English clinicians confirmed the generalisability of the BOREAS and NOTUS trial populations to the COPD patient population in England with high EOS levels.(167)

- **Patients enrolled in BOREAS and NOTUS were predominantly White**

Despite efforts to enrol a diverse patient population, 86.9% of participants enrolled in the BOREAS and NOTUS trials were White.(174) Pre-planned subgroup analyses by race, however, confirmed that dupilumab demonstrated consistent clinical benefit in terms of moderate or severe exacerbation reduction and change in pre-BD FEV_1 across different demographic groups.(168, 169, 174)

- **BOREAS and NOTUS did not collect long-term data on HRQoL**

Limited EQ-5D data were collected during the BOREAS and NOTUS trials. In BOREAS, EQ-5D data were collected only at baseline, while in NOTUS, EQ-5D data were collected at baseline, Week 24 and Week 52.(168, 169)

In both trials, the health status and HRQoL of participants was assessed using the SGRQ.(168, 169) An established mapping algorithm published by Starkie et al. in 2011 can be used to map SGRQ scores from both studies to EuroQoL 5-dimension 5-level (EQ-5D-5L) outcomes.(187) However, further analysis indicated that this study had some methodological limitations and did not fully align with the baseline EQ-5D-5L data from BOREAS and NOTUS. (For example, at baseline, utility was 0.71 in the studies (5L cross-walked to 3L) but using the Starkie algorithm to map SGRQ to EQ-5D-3L baseline utility was estimated to be 0.66. See Appendix Q). Consequently, we developed our own mapping algorithm to convert SGRQ to EQ-5D for use in the economic model (Section B.3.4.4).(188)

- **BOREAS and NOTUS were conducted during the Ukraine/Russia conflict**

In February 2022, when the conflict between Ukraine and Russia escalated, both the BOREAS and NOTUS trials were still ongoing.(170, 171) During this time, 22 participants in Ukraine and 2 participants in Russia in the BOREAS trial and 32 participants in Ukraine and 44 participants in

Russia in the NOTUS trial were receiving study intervention.(170, 171) All 24 participants in the BOREAS trial and 74 participants in the NOTUS trial (31 participants in Ukraine and 44 participants in Russia) completed the study.(170, 171) Therefore, the conduct and results of the trials were minimally impacted by the conflict.(170, 171)

B.3. Cost-effectiveness

Model Overview

- A cost-effectiveness analysis was conducted to evaluate dupilumab plus background therapy in comparison to background therapy alone from the perspective of the NHS in England for the treatment of uncontrolled COPD (≥2 moderate or ≥1 severe historical exacerbations within 12 months) with Type 2 inflammation (blood EOS ≥300 cells/μL).
- Following a review of the literature and the previous economic models considered by NICE for COPD, a cost-utility model structure was chosen consisting of a 1-year decision tree representing the study period followed by a long-term Markov model (cycle length 1 year over a lifetime horizon) including COPD severity stages (mild, moderate, severe and very severe airflow obstruction) along with recent exacerbation status as health states.
    - *Population:* Adults with uncontrolled COPD (≥2 moderate or ≥1 severe historical exacerbations within 12 months) and raised EOS (≥300 cells/μL; Type 2 inflammation) on triple inhaled therapy (LABA + LAMA + ICS) or double therapy (LABA + LAMA) where ICS is not appropriate. This reflects the full licensed indication for dupilumab in COPD as described in the scope and decision problem.
    - *Trial model inputs*: Clinical efficacy and safety data were taken from the pooled BOREAS and NOTUS phase 3 studies to make best use of the available data.
- EQ-5D was not collected consistently across the two studies but the St. Georges Respiratory Questionnaire (SGRQ) was available at all time points so mapped SGRQ-EQ-5D utilities were used in the model base case.
- Resource utilisation was based on the published NICE NG115 COPD economic model report, real world evidence (CPRD/HES) and clinical opinion where needed. Unit costs were derived from NHS Reference costs 2022/2023.
- The efficacy response criterion for continued treatment at 12 months considered a patient to be a non-responder if they experience more severe exacerbations on treatment than the year prior to treatment AND/OR, in the case of equal numbers of severe exacerbations, if they experience more moderate exacerbations than the year prior to treatment.
- Response waning is based on published rates for FEV_1 decline in patients with COPD, adjusted to reflect the documented accelerated lung function decline in the Type 2 COPD population.

Results

- The base case falls below the commonly accepted threshold for cost-effectiveness in England with a probabilistic incremental cost-effectiveness ratio (ICER) of £25,793 per quality-adjusted life-year (QALY) gained generated by the probabilistic analysis.
- Results were primarily driven by discontinuation rate, reference exacerbation rate at baseline, duration of lung function benefit post study, mortality and exacerbation risk.
- These ICERs were reasonably consistent across scenario and sensitivity analyses conducted indicating low decision uncertainty.

Conclusion

- Dupilumab is a clinically- and cost-effective use of NHS resources in patients with COPD and raised EOS (≥300 cells/μL blood eosinophil count; Type 2 inflammation) who have

uncontrolled disease (≥2 moderate or ≥1 severe historical exacerbations within the past 12 months) on maximal inhaled therapy.

- The clinical evidence, which shows an unprecedented reduction in exacerbations on top of background therapy, and the economic analysis highlight that dupilumab, which is the first licensed biologic in this therapy area, would address a significant unmet need for patients.
- Dupilumab also has the potential to relieve pressure on the healthcare system, particularly in the winter months when most exacerbations occur and the burden on respiratory services is at its highest.

B.3.1. Published cost-effectiveness studies

An SLR was conducted, searches were limited to studies published in English between January 2017 (the date of NICE's most recent COPD appraisal) to the cut-off date of 19 August 2024, to identify economic evaluations and cost-effectiveness studies of therapies in patients with uncontrolled COPD (Appendix G). In total, 599 records were identified from electronic database sources, including 310 records via Embase, 121 records via MEDLINE, 50 records via the Cochrane Central Register of Controlled Trials (CENTRAL), 19 records via the Cochrane Database of Systematic Reviews (CDSR) and 99 via EconLit. Following title/abstract and full-text screening, 36 publications were included in the SLR. A further six references were identified through hand searching of conference meetings and regulatory agencies, leading to a total of 42 records reporting on 35 unique economic evaluations.

Of the 35 economic evaluations identified by the SLR, most provided economic analyses from the UK (18 evaluations), Canada (5 evaluations) or Spain (4 evaluations). Other evaluations were from Sweden (3 evaluations), the US (2 evaluations), Finland, France and the Netherlands (1 evaluation each). Of the included studies, 21 assessed triple therapies (vs. monotherapy, double therapy or other triple therapy), with the remaining studies assessing double therapies. Most studies employed either a healthcare payer perspective (e.g., national health system payer) or a societal perspective.

B.3.2. Economic analysis

All of the economic evaluations identified by the SLR (Section B.3.1 and Appendix G) examined the cost-effectiveness of triple or double inhaled therapies in patients with uncontrolled COPD; none of the identified evaluations included patients with Type 2 inflammation (blood EOS ≥300 cells/μL), which is the target population for this submission.

Of the 35 economic evaluations identified in the SLR, 17 used the GALAXY model (described below) as their underlying structure, 11 used Markov, semi-Markov and Markov in combination with decision trees structures, one used both the GALAXY model and a decision tree plus Markov model, four used patient-level discrete-event simulation models, one used a patient-level microsimulation model and one did not report the model structure used.

Among the economic evaluations identified from the UK, one model from NICE was identified (Economic model report for inhaled triple therapy; NICE guideline NG115) which used a Markov

structure.(189) While not in the SLR scope (oral therapies were excluded), an additional Markov model for roflumilast was identified which was used in technology appraisal TA461 (roflumilast for treating COPD). This model follows a simple structure incorporating three health states (severe COPD, very severe COPD and death). The committee concluded that the model structure excluded some important aspects of COPD progression but it was considered adequate for decision-making.(133)

Both a Markov structure and the GALAXY structure, a regression-based model originally developed to assess the cost-effectiveness of inhaled therapies (not biologic treatments) based on the ECLIPSE trial population (patients with COPD and grade 2–3 airflow obstruction; as defined by GOLD and NICE),(190) were considered for this appraisal. Replicating the highly complex GALAXY model posed significant challenges; in particular, there was a lack of transparency regarding the model structure as the source code has not been published. Crucially, the GALAXY model does not allow for 'memory,' meaning it cannot account for the impact of prior exacerbations on future ones. While the GALAXY model incorporates prior exacerbations indirectly by influencing the risk of further exacerbations through lung function decline, it does not automatically adjust the exacerbation rate based on prior exacerbation history before randomisation. This is an essential feature for accurately capturing the natural history of COPD, as prior exacerbations are strong predictors of future exacerbations. Furthermore, as exacerbations were not a significant in the mortality equation of the GALAXY model, this structure was unlikely to capture the benefit of dupilumab observed for moderate and severe exacerbations (Section B.2). It is also likely that mortality rates were underestimated in the GALAXY model, as highlighted by Hoogendoorn et al. 2017.(191) Clinical experts consulted at an advisory board held by Sanofi in July 2024 with two health economists and five English clinicians with expertise in COPD (Section B.2.3.3),(167) recommended a Markov structure, considering it more transparent and easily understood than the GALAXY model. Given the limitations and issues around replicating the GALAXY model, as well as the endorsement by clinical experts and NICE committee acceptance of a Markov structure for TA46 (and use in NG115), we have chosen a Markov model structure as the most appropriate option to capture the benefits of dupilumab for the treatment of uncontrolled COPD characterised by Type 2 inflammation.

B.3.2.1. Key considerations for the CEM

Patients with COPD require lifelong treatment due to the chronic nature of the disease. Thus, it is important for the economic model to fully capture the costs and health outcomes associated with COPD management over a patient's lifetime. To represent the natural history of COPD patients over time, the cost-effectiveness model (CEM) needs to capture two key clinical aspects of the disease (among others, such as CV events and mortality associated with lung function decline and exacerbations):

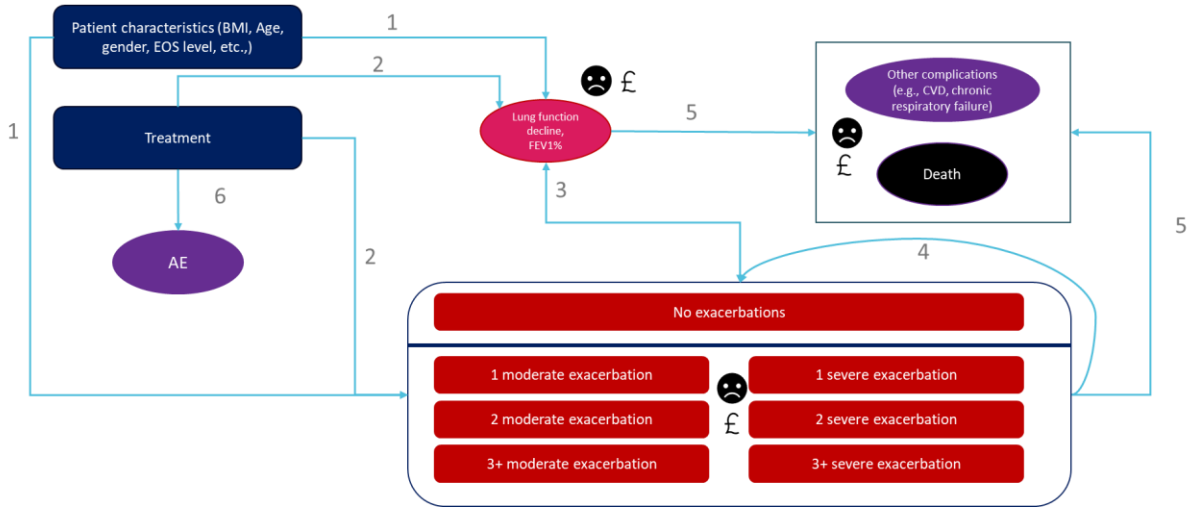
- **Lung function decline (reduction in FEV_1 percent predicted)**: 'FEV_1 percent predicted' is defined as the FEV_1 of the patient divided by reference FEV_1values adjusted for age, sex,

height and race, expressed as a percentage. Decline in FEV_1 percent predicted is considered a surrogate for the natural progression of COPD and treatments are often scrutinised on their impact on FEV_1 percent predicted over time. The 2024 GOLD global strategy and 2019 NICE guidelines classify the severity of airflow obstruction in COPD based on post-bronchodilator FEV_1 percent predicted as mild, moderate, severe or very severe COPD (as defined in Table 3; Section B.1.3.1).(3, 7) Other COPD economic models(192-194) follow this convention and have implemented health states based on these grades for severity of airflow obstruction.

- **Exacerbations**: Exacerbation events are characterised by acute worsening of symptoms and lung function, as well as being associated with mortality. Therefore, the model must incorporate evidence supporting the negative impacts of exacerbations on mortality,(26, 61) CV events,(86) rate of FEV_1 decline,(192, 195) as well as future exacerbation event risk.(26) In the 2024 GOLD global strategy, Groups C and D in the COPD assessment tool were combined into a single Group E, to reflect the clinical importance of exacerbations, independent of symptom burden (Figure 1; Section B.1.3.1).(3)

With these parameters in mind, a model influence diagram has been developed (Figure 23) to highlight the treatment effect on FEV_1 and exacerbations, as well as the relationship with other clinical parameters such as CV events and mortality.

Figure 23. Model influence diagram



AE = adverse events; BMI = body mass index; CVD = cardiovascular disease; EOS = blood eosinophil count; FEV_1 = forced expiratory volume; HCRU = healthcare resource utilisation; HRQoL = health-related quality of life
[1]Baseline patient characteristics affect lung function decline modelled as FEV_1% and risk of exacerbations.
[2]Treatment may improve lung function and reduce risk of exacerbation.
[3]Recent exacerbation history affects lung function decline and vice versa.
[4]Exacerbation history is a strong predictor of future exacerbations.
[5]Exacerbation history and lung function can affect other complications, and mortality.
[6]Treatments may be associated with AEs

In the UK, dupilumab is indicated as add-on maintenance treatment for uncontrolled COPD (≥2 moderate or ≥1 severe historical exacerbations within 12 months) in patients with Type 2 inflammation (blood EOS ≥300 cells/μL) on a combination of ICS, a LABA and a LAMA, or on a combination of a LABA and a LAMA if ICS is not appropriate.(1, 2) To fully capture the burden of uncontrolled COPD in

patients with Type 2 inflammation as well as the clinical benefits of dupilumab in this population, the model structure needs to consider the key relationships summarised in Table 33.

Table 33. Key considerations of the cost-effectiveness model for dupilumab in COPD

Parameters	Rationale
Lung function decline and exacerbation events	As disease management (HCRU) and utilities could depend on COPD severity, a lifetime model needs to capture lung function trajectory (measured as FEV_1) to reflect the progression of COPD over time and any impact of exacerbations.
Number and severity of exacerbations in the past year	Exacerbations are a key factor in the economic burden of COPD. Evidence exists to show that prior exacerbations (cumulative number and severity) are associated with future exacerbations.(196)
Effect of COPD on other clinical outcomes (cardiovascular events, chronic respiratory failure)	Patients with COPD have a higher prevalence of CV events (e.g., coronary heart disease, heart failure, heart attack) compared to those without COPD.(197) Fewer major adverse cardiovascular events were reported for dupilumab vs. placebo (0.7% vs. 1.7%) in the pooled BOREAS and NOTUS trial during the 52-week trial period.
Treatment effect is limited to trial duration of 52 weeks	The BOREAS and NOTUS treatment period only extend up to 52 weeks and thus whether the benefits of dupilumab can be maintained beyond 52 weeks is uncertain. The model needs to be flexible to allow testing of different assumptions around long-term FEV_1 benefit of dupilumab and allow for incorporating long-term efficacy outcomes if they become available in the future.
Use of external data to model long-term progression of COPD	Modelling disease progression for COPD cannot solely rely on the 52-week trial data. The model needs to incorporate appropriate external data to estimate outcomes beyond the trial follow-up period. In particular, to account for the impact of prior exacerbations on future exacerbation risk and also the natural decline in lung function.
Use of real-world evidence to inform exacerbation rates, standardised mortality ratios and HCRU	Data to reflect real-world UK patients that is not available from the clinical trials must be incorporated in the model. Exacerbation rates are often higher in the real world than observed in clinical trials and the treatment effect can be modelled by applying hazard ratios obtained from the studies to these real-world observed rates. The time horizon of the studies is not long enough to collect sufficient mortality data and so real-world evidence from UK databases must be used. HCRU is a key driver of the burden on the NHS; however, as UK HCRU data were not collected in the clinical trials, these data must be sourced externally.
Generalisability of external data to BOREAS and NOTUS populations	The BOREAS and NOTUS trial populations include patients with raised EOS (≥300 cells/μL) who received triple therapy (or double therapy if ICS was not appropriate). When incorporating external data, the generalisability to the BOREAS and NOTUS trial populations must be considered.

COPD = chronic obstructive pulmonary disease; CV = cardiovascular; ICS= inhaled corticosteroids; EOS = eosinophils; FEV_1 = forced expiratory volume in 1 second; HCRU = healthcare resource use

Based on the considerations listed above and the rationale provided in Section B.3.2, we have developed a cohort Markov model structure with a decision tree component representing the first year (trial period), which can accurately capture key aspects of the disease and treatment practices while reflecting the key trial endpoints and treatment effect of dupilumab. Our approach was endorsed at an advisory board held by Sanofi in July 2024 with five English clinicians with expertise in COPD and two health economists (Section B.2.3.3).(167)

B.3.2.2. Patient population

The population included in our CEM is adults with COPD with raised EOS (≥300 cells/μL) who have uncontrolled disease (≥2 moderate or ≥1 severe historical exacerbations within 12 months) on triple inhaled therapy (LABA + LAMA + ICS) or double therapy (LABA + LAMA) where ICS is not

appropriate. This reflects the indication for dupilumab in COPD as described in the scope and decision problem (Section B.1.1), the Summary of Product Characteristics(1) as well as the patient population in the BOREAS and NOTUS trials.(168, 169)

The base case analysis is conducted using the ITT population from the pooled BOREAS and NOTUS trials;(174, 177) two prespecified subgroups (FeNO ≥20 ppb; EOS ≥500 cells/µL) are explored in scenario analyses.

B.3.2.3. Cost-effectiveness model structure

The CEM was developed in Microsoft Excel® using a cohort Markov model structure with a decision tree component representing the first year (trial period).

Patients are distributed across the four health states defined by COPD severity stage at baseline in the trials (mild, moderate, severe and very severe; based on FEV_1 percent predicted; Table 3). The model begins with a decision tree to represent the first 52 weeks of treatment, informed directly by the trial outcomes. At the end of the decision tree period, patients are re-allocated to health states based on their 52-week COPD severity level in the trials (mild COPD, moderate COPD, severe COPD, and very severe COPD) and their exacerbation status (no exacerbation, recent moderate exacerbation, and recent severe exacerbation). At the end of the decision tree period, response assessment is considered, whereby patients who receive dupilumab + background therapy are characterised as responders or non-responders based on a response definition (Section B.3.3.2). The responders continue to receive dupilumab + background therapy, while the non-responders discontinue dupilumab and continue with background therapy (falling back to the outcomes and costs associated with background therapy alone). Beyond the trial period, a cohort Markov structure is used to model the long-term clinical and economic outcomes associated with dupilumab as an add-on to background therapy compared to background therapy alone.

The key rationale to include the decision tree component to model the trial period is that patients experience improvements in FEV_1 levels upon receipt of treatment during the trial period. As shown in Appendix S, FEV_1 levels in BOREAS and NOTUS trials improved from baseline in the first two weeks upon receipt of treatment. In addition, FEV_1 levels were maintained from Week 2 to the end of the trial period. Thus, a decision tree component split into an amelioration phase (the first two weeks) and maintenance phase most accurately reflects the observed data for calculating state occupancy (across severity of GOLD stages) at the end of two weeks and 52 weeks. Beyond 52 weeks (the observed trial period), the Markov component of the model takes over and no further transitions are associated with an improvement in FEV_1 (i.e., COPD severity can only deteriorate over time).

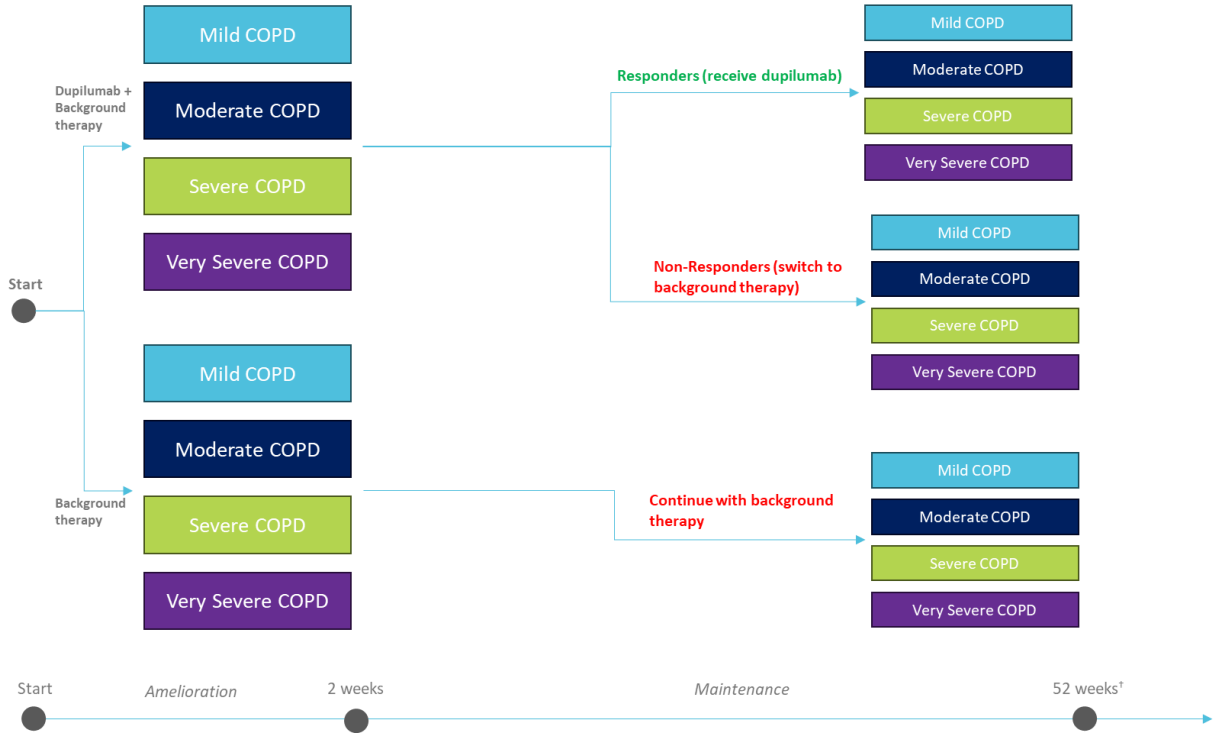
A half cycle correction is applied while accruing life-years, QALYs and costs in the model for both the trial period and the Markov period.

B.3.2.3.1. Decision tree (trial period) structure

The structure of the decision tree component, modelling the 52-week trial period, is depicted in Figure 24.

- At baseline (Week 0), patients are distributed across the four GOLD severity stages (mild, moderate, severe and very severe; as defined by GOLD and NICE; Table 3).
- State occupancy is determined separately for dupilumab + background therapy and background therapy alone at Week 2 (amelioration phase), based on either trial-observed data (base case) or treatment-specific transition probabilities (Section B.3.3.5).
- Similarly, the decision tree also calculates the state occupancy at Week 52 (maintenance phase), based on either trial-observed data directly or treatment-specific transition probabilities.

Figure 24. Decision tree structure (trial period)



†At 52 weeks, response is assessed in patients who receive dupilumab. Responders continue with dupilumab whereas non-responders discontinue dupilumab and only continue with background therapy
Mild COPD = FEV_1 ≥80% predicted, Moderate COPD = FEV_1 50-79% predicted; Severe COPD = FEV_1 30-49% predicted; Very Severe = FEV_1 <30% predicted
COPD = chronic obstructive pulmonary disease

The number of exacerbations experienced by patients in the trial period (stratified by moderate exacerbation and severe exacerbation) and the proportion of patients who experience ≥1 moderate exacerbation (without a severe exacerbation) and ≥1 severe exacerbation is either derived from the trial data or calculated based on treatment-specific transition probabilities. Since patients can experience more than one exacerbation in the trial period, the proportion of patients who have 1, 2

and ≥3 exacerbations (derived from the selected trial data) is used to stratify the patients further as illustrated in Table 34.

Table 34. Decision tree - stratification of patients at Week 52

Recent exacerbation status[a]	Notes
No exacerbation	Calculated based on the total proportion of patients summing to 1
≥1 moderate exacerbation[b]	Derived based on the moderate exacerbation rate (number of moderate exacerbations per year; without a severe exacerbation) from the selected trial and subpopulation
1 moderate only	The proportion of patients who have 1 moderate, 2 moderate, and ≥3 moderate exacerbations in the trial period is used to derive the number of patients at the end of 52 weeks based on the number of moderate exacerbations in the first year.
2 moderate only	
≥3 moderate only	
≥1 severe exacerbation[b]	Derived based on the severe exacerbation rate from the selected trial and subpopulation
1 severe	Similar approach as moderate exacerbation
2 severe	
≥3 severe	

Rates are applied to living patients only.
[a] The proportion of patients in the no exacerbation, ≥1 moderate exacerbation, and ≥1 severe exacerbation states are calculated for each COPD severity stage. It is also calculated separately for dupilumab + background therapy and background therapy arms. Patients on dupilumab + background therapy are split further into responders and non-responders at Week 52.
[b] The exacerbation rate is split into a moderate only exacerbation rate (without a severe exacerbation) and a severe exacerbation rate. This way, the percentage of patients in the ≥1 moderate exacerbation state would not have experienced any severe exacerbation in the past 1 year. However, patients in the ≥1 severe exacerbation state could have experienced multiple moderate exacerbations.

Key considerations of the trial period decision tree

- Response stratification: The model has the flexibility to assign patients receiving dupilumab + background therapy into responders and non-responders at the end of Week 52. This is applicable only for patients who receive dupilumab. Responders will continue to receive dupilumab and non-responders will switch to receive only background therapy beyond Week 52.
- Discontinuation: In addition to response stratification, patients receiving dupilumab can discontinue treatment and switch to receive only background therapy. For simplicity, since the decision tree component does not have a cycle length, it is assumed that the treatment discontinuation is applied as a one-off at the end of Week 52 (and not mid-way through the trial period). This is a conservative assumption as patients who discontinue in the first year still accrue costs for dupilumab until the end of Week 52. Beyond Week 52, the discontinuation group will receive only the background therapy in the Markov engine.
- Distribution of patients based on the number of exacerbations: The distribution of patients based on the number of exacerbations is a key input in the model as it determines the state occupancy at the start of the Markov model for each intervention. This is derived separately for dupilumab + background therapy and background therapy patients. The distribution of patients by the number of exacerbations derived from the trial period is assumed to be

constant throughout the Markov model horizon, due to the lack of data beyond the trial period. Hence, the distribution of patients stratified by the number of exacerbations is derived separately for responders and non-responders to dupilumab treatment, as shown in Table 35. Non-responders to dupilumab treatment are assumed to have this distribution based on background therapy.

Table 35. Distribution of patients based on the number of exacerbations

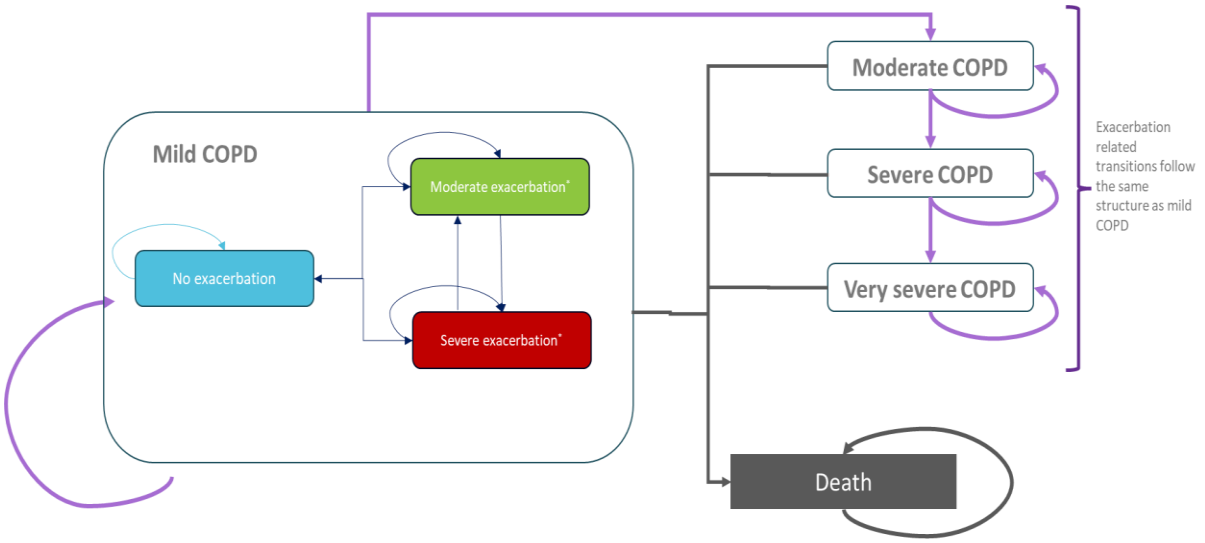
Recent exacerbation status	Dupilumab + Background Therapy			
	Mild COPD	**Moderate COPD**	**Severe COPD**	**Very severe COPD**
No exacerbation	Derived via moderate and severe exacerbation rate (all patients[a]; as described in Section B.3.2.3.2)			
≥1 moderate exacerbation	Derived via moderate and severe exacerbation rate (all patients[a]; as described in Section B.3.2.3.2)			
1 moderate	Proportion of patients with 1, 2, and ≥3 moderate exacerbations are derived separately for responders and non-responders.			
2 moderate				
≥3 moderate				
≥1 severe exacerbation	Derived via moderate and severe exacerbation rate (all patients; as described in Section B.3.2.3.2)			
1 severe	Proportion of patients with 1, 2, and ≥3 severe exacerbations are derived separately for responders and all non-responders[b]			
2 severe				
≥3 severe				

COPD = chronic obstructive pulmonary disease
[a] As response is not assessed until Week 52, exacerbation rates for all patients (rather than for responders vs. non-responders) are used for the trial period.
[b] Distribution of patients by number of exacerbations for non-responders to dupilumab treatment are assumed to be equal to the corresponding distribution of patients receiving background therapy. The distributions of 1, 2 and ≥3 exacerbations for non-responders and responders are used to calculate the distribution of patients stratified by the number of exacerbations at the start of the Markov period.

B.3.2.3.2. Markov (post-trial period) structure

The COPD GOLD severity stages (mild, moderate, severe and very severe COPD) along with recent exacerbation status (Table 35) are used as health states in the Markov model. There are three states based on patients' recent exacerbation status within each COPD severity stage (no exacerbation, moderate exacerbation and severe exacerbation), resulting in a 13-state Markov model including the self-absorbing death state. Within the Markov component, patients can only experience deterioration of their COPD severity over their lifetime and hence no transitions associated with amelioration are permitted as shown in Figure 25.

Figure 25. Markov model structure (post-trial period)



COPD = chronic obstructive pulmonary disease; Mild COPD = FEV_1 ≥80% predicted, Moderate COPD = FEV_1 50-79% predicted; Severe COPD = FEV_1 30-49% predicted; Very Severe = FEV_1 <30% predicted; Moderate exacerbation = treated with oral corticosteroids ± antibiotics; Severe exacerbation = requires hospitalisation or emergency department visits; may involve acute respiratory failure.
The starting health state occupancy at the beginning of the Markov model is derived from the trial period decision tree for each treatment.
* Moderate and severe exacerbation states are further divided into percentage of patients with 1, 2, or ≥3 exacerbations corresponding to the states at the end of the trial period engine. NOTE: CV events are not a separate health state but are treated similar to adverse events.

The health state occupancy at the beginning of the Markov model is derived from the trial period decision tree for each treatment. The Markov model has a cycle length of 1 year and assumes a lifetime time horizon (capped when the cohort reaches 100 years of age), although the model is sufficiently flexible to consider other user-defined horizons. At any given cycle, patients can experience two types of transition:

- **Transition within a COPD stage**: transitions associated with exacerbation
- **Transitions across COPD stages**: transitions associated with FEV_1 change (health states are based on FEV_1, e.g., mild COPD [FEV_1 ≥80% predicted] to moderate COPD [FEV_1 50% to 79% predicted]; as described in Section B.1.3.1.1)

Transitions within a COPD stage

At any given cycle, patients are in one of the seven exacerbation-associated states within a COPD stage, and they can experience one of the following events: ≥1 moderate exacerbation (without a severe exacerbation), ≥1 severe exacerbation, or no exacerbation. Because the cycle length is 1 year, patients can experience multiple exacerbation events and hence they are divided further into 1, 2 and ≥3 exacerbations, as shown in the Table 36. The transition probabilities are derived separately for each COPD stage based on the exacerbation rates stratified by COPD stage. The transition probabilities are treatment-specific and are derived based on the responder specific exacerbation rate for dupilumab patients since they continue with treatment in the Markov period.

Once patients transition to one of the exacerbation states (moderate exacerbation/severe exacerbation), patients are stratified into 3 groups based on the number of exacerbations (1, 2, and ≥3 exacerbations). This is done based on the trial-based distribution of patients in Table 35. Since dupilumab is informed via a RR vs background therapy, the distribution of patients based on the number of exacerbations in the dupilumab arm is conservatively assumed to be the same as background therapy.

Table 36. Summary of transitions within a COPD stage

Recent exacerbation status	No exacerbation	Moderate exacerbation[a]	Severe exacerbation[a]	Note
No exacerbation	Probability of patients not experiencing an exacerbation in a cycle	Probability of patients experiencing at least 1 moderate exacerbation (without severe exacerbation) in a given cycle	Probability of patients experiencing at least 1 severe exacerbation in a given cycle	Each row must sum up to 100%
1 moderate only				
2 moderate only				
≥3 moderate only				
1 severe				
2 severe				
≥3 severe				

COPD = chronic obstructive pulmonary disease
[a] Moderate exacerbation is further divided into 1, 2, and ≥3 moderate exacerbations based on the trial-based distribution of patients in Table 35. The same approach is followed for severe exacerbation as well.

Transitions across COPD stage

In addition to exacerbation-related transitions within the health states, patients can experience an increase in COPD severity over time. Patients transition between health states as their FEV_1 level breaches the upper threshold for a more severe state (Section B.3.3.6). The fact that exacerbations may cause a discrete FEV_1 decline is not explicitly considered.

The model has the flexibility to consider a slightly extended FEV_1 benefit at the start of the Markov portion of the model, beyond that observed in (and modelled for) the trial period. In this situation, the treatment effect of dupilumab + background therapy observed in the trial period, where FEV_1 levels remained stable during the maintenance period (Week 2 to Week 52), is assumed to hold in the FEV_1 treatment effect period (as described below). Beyond the FEV_1 treatment effect period, patients experience a natural decline in FEV_1 which informs the transitions across COPD stages. This aims to

reflect the added benefit of introducing a biologic to background therapy (see Section B.3.3.6 for further details).

Since the model has a cycle length of 1 year, the model makes a simplifying assumption that patients will experience the exacerbation probabilities associated with the destination COPD state. For example, if a patient with mild COPD and one recent severe exacerbation transitions to moderate COPD, then they will experience the exacerbation probabilities associated with moderate COPD and one recent severe exacerbation in a given cycle.

Mortality

In addition to transitions within and across COPD stages, patients can experience death events and transition to the absorbing death state. In this case, patients remain in the death state and subtracted from the model trace at each cycle. Mortality risk is stratified by COPD stage and recent exacerbation status (Section B.3.3.8).

Cardiovascular events

As patients with COPD have an elevated risk of experiencing CV events (Section B.1.3.1.3), the impact of CV events is modelled as an adverse event. The risk of experiencing a non-fatal CV event is stratified by a patients' exacerbation status. During the trial period, the CV risk is treatment-specific and is derived directly from the pooled BOREAS and NOTUS trials, while the incidence of CV events in the Markov period (stratified by exacerbation-related states) is derived from a post-hoc analysis of the large international SUMMIT RCT, in lieu of relevant UK data (Section B.3.5.3.3). Fatal CV events are not considered in the model due to their very low incidence.

Adverse events

Patients in the model can experience AEs in every cycle, and the costs and disutilities associated with these AEs are calculated (Section B.3.5.4).

B.3.2.3.3. Model features

The base case analysis is conducted from the perspective of the UK National Health Service (NHS). The time horizon in the analysis is a lifetime, which is defined as the time until the cohort reaches 100 years of age. This time horizon is considered sufficient to capture the long-term clinical and economic impacts of COPD, while limiting uncertainty inherent in projecting health outcomes beyond the trial period. Costs and health-related outcomes are discounted at a rate of 3.5% in the base case in accordance with NICE guidance.(198)

A summary of the features of the economic analysis for dupilumab as well as a comparison to the only previous NICE HTA for COPD (TA461, roflumilast) are summarised in Table 37.

Table 37. Features of the economic analysis

Factor	Previous appraisal	Current evaluation	
	TA461 (roflumilast)	**Chosen values**	**Justification**
Model structure	Markov model (3 health states)	Markov model (12 health states plus an absorbing death state) with a decision tree component in the first year (trial period)	Best use of available data; captures key aspects of the disease and treatment practices
Patient population	Patients with severe COPD, chronic bronchitis and ≥2 exacerbations in the previous year	Adults with COPD and raised EOS (≥300 cells/μL) who have uncontrolled disease (≥2 moderate or ≥1 severe historical exacerbations within 12 months) on triple inhaled therapy (LABA + LAMA + ICS) or double therapy (LABA + LAMA) where ICS is not appropriate	Reflects the indication for dupilumab in COPD as described in the scope and decision problem, the SmPC, as well as the patient population in the BOREAS and NOTUS trials.
Time horizon	NR	Lifetime (35 years)	NICE guidance(198) Given the median age of 65 years for the patient population in BOREAS and NOTUS, 35 years is a fair approximation of a lifetime horizon
Perspective	NHS	NHS	NICE guidance(198)
Discounting	NR	3.5%	NICE guidance(198)
Cycle length	1 month	1 year	To reflect the progressive nature of COPD and account for the extended recovery time from severe exacerbations, which impact patient quality of life and aggregate costs over several months.(199)
Treatment waning effect	NR	Dupilumab + background therapy- 2 year; background therapy - 0 year	TRAVERSE study in asthma which shows that lung function benefit was maintained for two years following exit from the RCTs (which lasted 1 year).
Source of utilities	COPD severity from Rutten van Molken (2006)(200) Disutilities from Rutten van Molken (2009)(201)	Mapped SGRQ to EQ-5D from the pooled BOREAS and NOTUS studies	Limited EQ-5D data were collected in the studies (see Section B.2.3.1). The main source of EQ-5D trial data comes from NOTUS but this study was stopped early when the primary end point was reached. Hence the dataset for EQ-5D does not contain all patient outcomes. SGRQ was collected in both studies at all time points so to make best use of the trial data we have chosen to use the SGRQ data mapped to EQ-5D (Section B.3.4.2).
Source of costs	NR	Resource use frequencies and unit costs for health states and moderate exacerbations are derived from the NICE NG115 COPD	Resource use frequencies for health states and moderate exacerbations are in line with the 2018 NICE COPD economic model report.(189)

Factor	Previous appraisal	Current evaluation	
	TA461 (roflumilast)	Chosen values	Justification
		economic model report, with unit costs from NHS Reference Costs 2022/23. Resource use frequencies for severe exacerbations are derived from the HES database, with unit costs from NHS Reference Costs 2022/23.	Resource use frequencies for severe exacerbations are derived from the HES database due to the lack of granularity in the published literature.(123)

COPD = chronic obstructive pulmonary disease; EOS = eosinophils; HES = hospital episode statistics; ICS = inhaled corticosteroids; LABA = long-acting β2 agonist; LAMA = long-acting muscarinic antagonist; NHS = National Health Service; NICE = National Institute of Healthcare and Excellence

B.3.2.4. Intervention technology and comparators

In the BOREAS and NOTUS trials, and in line with the MHRA SmPC, dupilumab was administered as a 300 mg subcutaneous dose every two weeks in combination with background therapy (triple therapy or double therapy if ICS is not appropriate).(1, 168, 169) The model therefore includes the same dosing and administration for dupilumab. Over 95% of patients enrolled in the dupilumab trials were on triple background therapy. NICE guidelines recommend triple therapy for patients where symptoms adversely impact their quality of life, or they experience a severe or 2 moderate exacerbations.(7) The latest GOLD global strategy (Section B.1.3.2.2) recommends escalation to triple therapy for patients in GOLD group E who have EOS ≥300 cells/μL.(3, 202) Therefore, the base case uses a within-trial comparison mainly comprised of triple therapy (or double therapy if ICS is not appropriate), as this is the most relevant comparator. The various comparators used in the model are discussed below.

B.3.2.4.1. Triple therapy (or double therapy if ICS is not appropriate).

The model considers background therapy as a weighted comparator of ICS + LAMA + LABA (or LAMA + LABA if ICS is not appropriate). Due to the availability of a variety of different inhaled therapies in England, and the variability in prescription practices according to the individual needs of patients, it is appropriate to consider background therapy as a basket of therapies for costing purposes. The treatments included as part of the background therapy comparator basket are listed in Table 38, based on 2023 data from IQVIA's Hospital Pharmacy Audit (HPA).

Table 38. Market shares for background therapy

Background therapies	Administration regimen	Market share (%)
Trelegy Ellipta (fluticasone/umeclidinium/vilanterol)	1 inhalation daily	38.0
Trimbow NEXThaler (beclomethasone/formoterol/glycopyrronium)	2 inhalations twice daily	59.4
Trimbow (beclomethasone/formoterol/glycopyrronium)	2 inhalations twice daily	
Trixeo aerosphere (budesonide/formoterol/glycopyrronium)	2 inhalations twice daily	2.6

The market share for the triple therapy inhalers is calculated based on the average pack sales from January to December 2023, using IQVIA Hospital Pharmacy Audit data.
Source: Sanofi 2024 [Data on File] COPD IQVIA Hospital Pharmacy Audit(203)

As the background therapy is consistent in both arms of the model, we have only looked at triple combination inhalers and derived the market shares of these only to simplify the analysis.

B.3.2.4.2. Roflumilast

For patients with uncontrolled COPD on triple therapy (or double therapy if ICS is not appropriate), the NICE 2019 guidelines and GOLD 2024 global strategy recommend the use of roflumilast for patients with FEV_1 <50% predicted and ≥2 exacerbations in the last year or add-on therapy with azithromycin for non-smokers (Section B.1.3.2.3).(3, 7) Whilst roflumilast is recommended by NICE, and for that reason could be considered a relevant comparator, in practice, data show it is rarely used and is not a durable maintenance treatment, and therefore we do not think this comparison is relevant to clinical practice in England, as set out below (see also Appendix T for further information):

1. *The overlap between the roflumilast and dupilumab target populations is limited.*

    - Roflumilast is approved as add-on to triple therapy for patients with <50% FEV_1 predicted who have a history of exacerbations and chronic bronchitis despite optimal bronchodilator therapy.
    - Dupilumab targets patients with uncontrolled COPD (≥2 moderate or ≥1 severe exacerbations within 12 months) with Type 2 inflammation (≥300 EOS/µL), despite triple therapy (or double therapy when ICS is not appropriate). The studies (and consequently the label) included patients with FEV_1 predicted ≥50% i.e., dupilumab is indicated in a wider group of patients, including those with moderate disease (FEV_1 predicted 50% to 79%).

2. *Very low clinical use and uptake means roflumilast is not standard care.*

    - We have spoken to several clinical experts about the validity of carrying out a comparison with roflumilast, all of whom confirmed that roflumilast is rarely used, if at all, in their clinical practice so cannot be defined as standard care. We have provided an overview of prescribing in Section B.1.3.2.3 (see Figure 10 which shows prescribing is limited to a few areas). They have expressed concerns about the efficacy and safety of roflumilast, citing these reasons for its very low uptake.
    - GP prescribing data for England supports the assertion that roflumilast is not standard care. The data indicates that, on average between 2020 and 2023, only 909 patients per year were initiated with roflumilast and stayed on for 8 months (Section B.1.3.2.3).(139)

3. *There are significant technical challenges when making comparisons between the pooled roflumilast REACT and RE2SPOND studies and the pooled dupilumab BOREAS and NOTUS studies due to evolving medical practice.*

Given the inclusion of roflumilast in the scope and extant NICE guidance (TA461), and in the absence of head-to-head RCTs comparing the efficacy of dupilumab to other treatment options, a feasibility assessment was conducted to explore whether an ITC could be used to estimate the comparative efficacy of dupilumab against roflumilast (Section B.2.9 and Appendix D). The feasibility assessment

concluded that it is not possible to conduct an ITC due to the differences in study designs and placebo arms between the dupilumab and roflumilast trials. The findings are summarised below:

- The placebo arm is not the same for the studies: background therapy in the pooled REACT and RE2SPOND analysis included double (42%) and triple therapy (58%) whereas in BOREAS 97.6% of the placebo arm were on triple background therapy. No adjustment based on the type of background therapy results were provided by the authors for the pooled roflumilast analysis (Martinez et al. 2018),(140) which is essential for comparative purposes as triple therapy has demonstrated greater efficacy to double therapy.
- The patient populations are different:
    - The REACT and RE2SPOND trials and pooled analysis included patients with severe and very severe COPD (<50% predicted FEV_1) whereas the BOREAS trial included patients with moderate and severe COPD (approximately 50% in each severity stage)
    - Patients with Type 2 inflammation (raised EOS levels) were a subgroup of the REACT and RE2SPOND trials. While the subgroup analysis of this study is published (Martinez et al. 2018),(140) there are no publicly available data for the patients with high EOS on triple therapy only

When comparing treatments, several key assumptions around transitivity, consistency and homogeneity must be met to ensure validity of the ITC results. As described above and in Section B.2.9, there are a number of substantial differences between the roflumilast and dupilumab trials that prohibit the conduct of a credible ITC. Despite this, an exploratory ITC has been undertaken to address the inclusion of roflumilast in the final NICE scope (Section B.2.9 and Appendix D). We have also undertaken an analysis to estimate the effect size of roflumilast on top of triple therapy alone for patients with raised blood EOS as these data are not available (Section B.2.9 and Appendix D). These analyses are highly exploratory and should be treated with caution but do highlight significant uncertainty in providing a robust estimate for the treatment effect in this population.

We have included these data in the economic model but believe this should be considered no more than a highly uncertain exploratory analysis and no meaningful conclusions should be drawn from the results (Section B.3.11.3).

B.3.2.4.3. Azithromycin

Azithromycin was not included in the draft scope but was added after the scoping consultation and invitation to participate, leaving limited time to produce a comparative assessment. Azithromycin is not licensed for the treatment of patients with COPD in England and carries no NICE technology appraisal guidance for COPD, although off-label use is recommended in the NICE 2019 guidelines to be considered as prophylaxis (Section B.1.3.2.3).(7) We do not believe that azithromycin is a valid comparator for this appraisal and have not provided a comparison for the following reasons:

1. *The overlap between the azithromycin guidelines and the dupilumab label is limited.*

There is no UK label for azithromycin in COPD and limited overlap between the azithromycin population in the NICE 2019 guideline recommendation and the label population for dupilumab. The NICE guidelines limit the azithromycin population to only patients who are non-smokers and continue to experience ≥4 exacerbations per year despite optimised inhaled treatment (double or triple therapy).(7, 149) This is a restricted population compared to the dupilumab label and submitted population in this appraisal (which includes former or current smokers with ≥2 moderate exacerbations or ≥1 severe exacerbation in the previous year).(1, 2)

Azithromycin lacks specific clinical evidence in patients with uncontrolled COPD and Type 2 inflammation, has very limited evidence to support its use as add-on to triple therapy and there is no evidence to support the efficacy and safety in COPD beyond one year of treatment.(3-5)

2. *In COPD patients, azithromycin has been associated with a significant increase in antibiotic resistance.*

Macrolide resistance is rapidly inducible, highly transferrable and increasing in prevalence in line with increasing macrolide prescriptions.(4, 12, 155, 204) It is therefore critical that any analysis and potential NICE recommendation (actual or implicit) would not be seen to further endorse the off-label use of an agent whose use in the maintenance treatment of COPD is associated with increased levels of AMR. This would be inconsistent with the antimicrobial stewardship aims of the WHO, EMA, NHS England and NICE.

Azithromycin has been associated with a significant increase in antibiotic resistance.(4, 12, 155, 204) A meta-analysis of studies across COPD, cystic fibrosis, bronchiectasis and asthma has shown that long-term treatment with azithromycin increases the incidence of antibiotic resistance by 2.7 times versus placebo.(155) In patients with COPD specifically, azithromycin increased the incidence of antibiotic resistance by up to 3.76 times (i.e., +276%) versus placebo.(155) Another study found an increase in resistant bacteria in 81% of COPD patients treated with azithromycin, versus 41% with placebo.(4) A study of long-term azithromycin usage has suggested that development of AMR may result in waning of efficacy over time.(156) Indeed, a study in patients with stable COPD demonstrated that an approximately 6-fold higher concentration of azithromycin is required to achieve microbicidal effect post-treatment compared with the concentration required pre-treatment.(12)

The GOLD 2024 global strategy highlights the risk of developing AMR associated with the use of azithromycin with the maximum level of evidence (level A).(3) Due to concerns with rising AMR, azithromycin is currently under review by the EMA with the aim of restricting its use.(13) It has also been classified by the World Health Organization (WHO) as an antibiotic that carries a higher risk of AMR and is included in WHO's Watch list (AWaRe classification).(205)

AMR and its associated burden remain a key concern of the UK government.(13, 14) In 2022, an estimated 58,224 people in England had an antibiotic-resistant infection, a 4% increase from 2021.(14) Deaths from severe antibiotic-resistant infections also increased from 2,110 to 2,202 over the same period.(14) The National Action Plan, 'Confronting antimicrobial resistance 2024 to 2029', contains outcomes and commitments towards the 20-year vision of ensuring that AMR will be controlled and contained by 2040.(206) The National Action Plan includes elements encouraging doctors to prescribe macrolides only when necessary or when they are the most appropriate treatment option, and to regularly review patients on long-term therapy.(206) NICE also offer guidelines (NG15) and a quality standard (QS121) to promote "antimicrobial stewardship" in England.(159, 160)

3. *Azithromycin does not directly target the underlying pathophysiology of COPD, as its mechanism of action targets bacterial infections.*

As an antibiotic, azithromycin inhibits bacterial protein synthesis.(151) Bacterial infection is associated with approximately 50% of acute exacerbations of COPD,(152) and therefore prophylactic azithromycin may reduce the risk of bacterial infection and associated neutrophilic airway inflammation, reducing exacerbation risk.(153) Even though the specific mechanism of action for azithromycin remains unclear, it does not target the underlying pathophysiology of COPD.(151) Additionally, long-term treatment with macrolides has been shown to significantly increase the Type 2 inflammatory mediators (e.g., IL-4, and IL-13) that are targeted by dupilumab.(154)

4. *Technical issues with providing a robust comparison.*

Similar to the comparison with roflumilast, there are key challenges in developing a robust ITC between dupilumab and azithromycin:

- **The placebo arm is not the same for the published studies:** There are several published azithromycin studies but most are small and short term (12 to 26 weeks) examining far fewer than 100 patients.(10-12, 153) The two published 52-week studies are limited by overall patient numbers(9) and/or the proportion of patients on background triple therapy.(4) No studies provide subgroup analyses for patients on background triple therapy.
- **No subgroup defined by EOS level is available:** No studies provide analysis for patients with high EOS counts (>300 cells/µL).

We have been unable to identify an appropriate source which can provide a robust counterfactual.

In summary, azithromycin and dupilumab are fundamentally different types of medications and have been studied and recommended in COPD populations with very limited overlap, which would make direct or indirect comparisons challenging and unlikely to provide meaningful or robust data for use in an economic model. Furthermore, considering the risks of development of AMR with azithromycin and

global aims of antimicrobial stewardship, a NICE endorsement of azithromycin use in COPD would be inappropriate. We have therefore not conducted an analysis comparing dupilumab and azithromycin.

B.3.3. Clinical parameters and variables

In the base case, clinical inputs for dupilumab and background therapy are based on a post-hoc analysis of pooled patient-level data from the BOREAS and NOTUS trials (hereafter referred to as the ITT population unless otherwise stated; Section B.2.4.3).(207) A separate statistical analysis plan was developed to derive the clinical outcomes required for the model, e.g., exacerbation rates, FEV_1 change over time, GOLD severity during the trial period. The following sections focus on describing the inputs used in the base case. Detailed information on inputs used in scenario and subgroup analyses are provided in Appendix N.

B.3.3.1. Distribution of patients by GOLD severity (GOLD grade)

The distribution of patients by GOLD severity at the end of the FEV_1 amelioration phase (i.e., Week 2) and the end of the FEV_1 maintenance phase (i.e., Week 52) is derived for the ITT population by treatment arm. The baseline distribution is based on the average of the two treatment arms combined. The distribution probabilities for the ITT population are presented in Table 39.

Table 39. Distribution of patients by GOLD severity by treatment (ITT population)

Timepoint	Proportion of patients (%)							
	Dupilumab + Background Therapy				Background Therapy			
	Mild	Moderate	Severe	Very Severe	Mild	Moderate	Severe	Very Severe
Baseline	2.4	47.0	47.7	3.0	2.4	47.0	47.7	3.0
Week 2	7.2	49.6	39.3	3.9	4.3	51.3	40.5	4.0
Week 52	10.0	44.2	40.5	5.4	5.6	46.6	42.4	5.4

GOLD = Global Initiative for Chronic Obstructive Lung Disease; ITT = intention-to-treat
Source: Sanofi 2024 [Data on file] Pooled analysis - Post-hoc analyses for CE model(207)

The model provides the flexibility for patients to start at different GOLD severity stages from the trial population. The conditional probabilities based on GOLD severity at Week 2 derived from trials are applied to project the cohort's distribution by GOLD severity at Week 2. The conditional probabilities for the ITT population are presented in Table 40.

For the maintenance stage (from Week 2 to 52), no change of GOLD severity is assumed.

Table 40. Conditional probabilities by GOLD severity at Week 2 by treatment (ITT population)

Start state	End state (%)							
	Dupilumab + Background Therapy				Background Therapy			
	Mild	Moderate	Severe	Very Severe	Mild	Moderate	Severe	Very Severe
Mild	73	27	0	0	47	53	0	0
Moderate	9	81	10	1	4	88	9	0
Severe	3	23	69	5	3	16	75	5
Very Severe	5	0	55	41	0	0	37	63

GOLD = Global Initiative for Chronic Obstructive Lung Disease; ITT = intention-to-treat
Source: Sanofi 2024 [Data on file] Pooled analysis - Post-hoc analyses for CE model(207)

B.3.3.2. Responder rates

COPD is a progressive disease characterised by decline in lung function and exacerbations which are predictive of further exacerbations in the future. Therefore, stabilisation of disease is a good outcome for these patients with Type 2 inflammation who continue to exacerbate whilst on maximal inhaled therapy. The efficacy response criterion used in the model reflects this. In the base case, a patient is considered a non-responder if they experience more severe exacerbations than the year prior to treatment AND/OR, in case of equal number of severe exacerbation if they experience more moderate exacerbations than the year prior to treatment. All other cases are considered responders.

This efficacy response criterion was tested with clinicians at the advisory board, and they suggested a simple rule should be chosen to reflect maintenance of stable disease, which is a good outcome for patients, and would be a response criterion that could be implemented.(167)

Based on this, the response rate among patients who receive dupilumab + background therapy at the end of Week 52 is 94.2% for the ITT population.

In the base case, the model applies a response assessment at the end of Week 52 of treatment with dupilumab, assuming responders continue receiving dupilumab + background therapy while non-responders switch to receiving background therapy only, however, in clinical practice patients who do not respond might be identified sooner. In the long-term model (after Week 52), clinical outcomes specific to responders are applied, while clinical outcomes related to background therapy are applied to non-responders.

Response assessment is not applied to the background therapy arm.

B.3.3.3. Exacerbation rates

Clinical experts consulted by Sanofi at an advisory board in August 2024 highlighted that the rate of exacerbations observed in clinical trials often differs from those observed outside of a trial setting.(167) This discrepancy may be due to differences in patient adherence influenced by the protocol driven nature of clinical trials, as well as the assessment and reporting of exacerbation events.

B.3.3.3.1. Baseline exacerbation rates

To mitigate the expected low exacerbation rates observed in clinical trials compared with the real world while keeping as closely as possible to the trial population data, we have used patient data (placebo and dupilumab combined) from the year prior to randomisation as the baseline exacerbation rate in the base case (Table 41). Most patients entered the studies on a background of triple therapy with exacerbation history provided.

A sensitivity analysis uses baseline exacerbation rates from the real-world setting. However, the study population data prior to trial entry are considered more appropriate as the treatment effect of dupilumab is based on this population (uncontrolled on background triple therapy and Type 2 inflammation). These rates are likely to more closely represent real-world clinical practice for this patient population.

Table 41. Annualised exacerbation rates by GOLD severity for background therapy derived from the year prior to randomisation

GOLD severity	Background Therapy - All Patients	
	Moderate Exacerbation	Severe Exacerbation
Mild	1.8	0.2
Moderate	1.9	0.3
Severe	2.0	0.3
Very Severe	2.0	0.4

GOLD = Global Initiative for Chronic Obstructive Lung Disease
Source: Sanofi 2024 [Data on file] Pooled analysis - Post-hoc analyses for CE model(207)

B.3.3.3.2. Exacerbation rates

The exacerbation rates for dupilumab + background therapy in the model are informed by the relative risk of exacerbation observed during the study period (Week 2 to Week 52) from the pooled analysis of BOREAS and NOTUS (Table 42). The exacerbation rates are stratified by the GOLD severity observed at Week 2 of the trial. In addition, exacerbation rates are stratified by patients' responder status at Week 52 according to the efficacy response criterion discussed in Section B.3.3.2. Given the small number of patients with either mild or very severe GOLD severity and with ≥1 moderate or severe exacerbation during the first 52 weeks of treatment (approximately 20 patients in each grade per pooled treatment arm), observed annualised exacerbation rates are not further adjusted for potential confounders (e.g., baseline disease severity, smoking status at screening, number of exacerbations within 1 year before the study). Unadjusted annualised exacerbation rates are used directly. In the dupilumab + background therapy arm, exacerbation rates are recorded for all patients as well as for responders only (Table 43).

Table 42. Relative risk for exacerbation by GOLD severity of dupilumab + background therapy vs. background therapy (ITT population)

GOLD severity	Dupilumab + Background Therapy			
	All Patients		Responders	
	Moderate Exacerbation	Severe Exacerbation	Moderate Exacerbation	Severe Exacerbation
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]
Very Severe	[redacted]	[redacted]	[redacted]	[redacted]

GOLD = Global Initiative for Chronic Obstructive Lung Disease; ITT = intention-to-treat
Source: Sanofi 2024 [Data on file] Pooled analysis - Post-hoc analyses for CE model(207)

Table 43. Annualised exacerbation rates by GOLD severity for dupilumab + background therapy derived from the clinical trials (ITT population)

GOLD severity	Dupilumab + Background Therapy			
	All Patients		Responders	
	Moderate Exacerbation	Severe Exacerbation	Moderate Exacerbation	Severe Exacerbation
Mild	0.24	0.02	0.19	0.00
Moderate	0.44	0.04	0.39	0.01
Severe	0.77	0.07	0.60	0.02
Very Severe	0.81	0.07	0.69	0.02

GOLD = Global Initiative for Chronic Obstructive Lung Disease; ITT = intention-to-treat
Source: Sanofi 2024 [Data on file] Pooled analysis - Post-hoc analyses for CE model(207)

To explore the impact of baseline exacerbation rates on the model results, sensitivity analyses have been conducted using:

- RWE exacerbation rates taken from the CPRD-HES database.(59)
    - Baseline exacerbation rate is an important driver of cost-effectiveness, so to inform baseline exacerbation for UK patients in the real world, a CPRD-HES study was performed.(59) This study included patients who were as closely aligned with the dupilumab study populations as possible:(59)
        - People with COPD[xii], who aligned with the BOREAS population (as closely as could be determined from EHR):
            - Current or former smokers
            - Moderate-to-severe COPD (post-bronchodilator FEV_1/ FVC ratio <0.70 and post-bronchodilator FEV_1% predicted >30% and ≤70%).
            - Medical Research Council (MRC) Dyspnea Scale grade ≥2.
            - Evidence of chronic bronchitis
            - Background triple therapy (ICS + LABA + LAMA)

[xii] Note, the HES-CPRD study included both controlled and uncontrolled patients. Data for the uncontrolled cohort were used in the cost-effectiveness model.

        - Evidence of Type 2 inflammation: Patients with blood eosinophils ≥300 cells/microliter
    - Annualised exacerbation rates for these patients were derived from the study and used in scenario analysis (adjusted by GOLD stage using Wallace et al. 2019).(208)
- Trial-based rates, using the unadjusted annualised rates from the background therapy arm in the pooled analysis of BOREAS and NOTUS

The inputs used in these sensitivity analyses are provided in Appendix N.

B.3.3.4. Distribution of patients by number of exacerbations

To better capture the costs and disutilities associated with exacerbations, patients residing in the 'Moderate Exacerbation' or 'Severe Exacerbation' health states are further stratified by the number of exacerbations (1, 2, or ≥3). This is because the model cycle length of 1 year is sufficiently long for several exacerbations (moderate or severe) to occur. The proportions of patients experiencing different numbers of exacerbation events is taken from the 52-week study period according to the pooled analysis (Table 44).

Table 44. Proportion of patients experiencing exacerbations by treatment for the ITT population

No. of Exacerbations	Proportion of patients (%)					
	Dupilumab + Background Therapy				Background Therapy	
	All Patients		Responders			
	Moderate Exacerbation	Severe Exacerbation	Moderate Exacerbation	Severe Exacerbation	Moderate Exacerbation	Severe Exacerbation
0	66.1	96.3	73.4	98.2	58.8	93.6
1	20.7	3.1	22.4	1.8	22.5	5.3
2	8.4	0.4	3.1	0.0	9.6	0.8
≥3	4.7	0.2	1.1	0.0	9.1	0.2

ITT = intention-to-treat
Source: Sanofi 2024 [Data on file] Pooled analysis - Post-hoc analyses for CE model(207)

Furthermore, trial data are used to estimate the average number of exacerbations for patients who have ≥3 exacerbations. As patients who are assigned to the severe exacerbation category may also experience moderate exacerbations, the average number is also informed by the trial data (Table 45). For example, a patient with one severe exacerbation is assumed to experience one moderate and one severe exacerbation on average, whereas a patient with ≥3 severe exacerbations is assumed to experience one moderate and 3.75 severe exacerbations on average.

Table 45. Average number of exacerbations for each exacerbation state

Sub-state defined by no. of exacerbations	No. of moderate exacerbations	Source	No. of severe exacerbations	Source
1 moderate only	1	Assumption to reflect the definition of the substate	0	Assumption to reflect the definition of the substate
2 moderate only	2		0	
≥3 moderate only	3.84	Pooled trials	0	
1 severe	1		1	
2 severe	1		2	
≥3 severe	1		3.75	Pooled trials

Source: Sanofi 2024 [Data on file] Pooled analysis - Post-hoc analyses for CE model(207)

B.3.3.5. Transition probabilities within a COPD stage

Within each COPD stage, patients may experience no exacerbation, ≥1 moderate exacerbation (without severe) or ≥1 severe exacerbation in each cycle. The transition probabilities within COPD stages are determined by the patient's residing COPD stage and recent exacerbation history (i.e., no exacerbation, moderate exacerbation, or severe exacerbation in the prior year).

No granular data are available from the dupilumab trials or RWE to inform the subsequent exacerbation risk associated with the frequency of prior exacerbations. Whittaker et al. 2022 reported adjusted incidence rate ratios for patients with 1, 2 and ≥3 exacerbations compared with no exacerbations (stratified by severity of exacerbations), using data from the CPRD database.(26) These published data are further stratified by patients with EOS ≥300 cells/µL which allows for better alignment with the target population of this submission (Table 46). The reference exacerbation rates for 'no prior exacerbation' from Whittaker et al. 2022 are not stratified by GOLD stage; a moderate exacerbation rate of 0.64 and severe exacerbation rate of 0.126 was reported for these patients.(26) The exacerbation rates for patients with no recent prior exacerbation by GOLD stage are therefore sourced from Wallace et al. 2019 (Table 47).(208)

Table 46. Adjusted incidence rate ratios for future moderate and severe exacerbations by baseline frequency and severity of exacerbation in patients with EOS ≥300 cells/µL

Prior Exacerbation Status	Adjusted IRR (95% CIs)	
	Moderate Exacerbation	Severe Exacerbation
No exacerbation	1 [reference]	1 [reference]
1 moderate only	1.78 (1.70, 1.86)	1.21 (1.12, 1.31)
2 moderate only	2.44 (2.32, 2.58)	1.38 (1.25, 1.53)
≥3 moderate only	3.94 (3.75, 4.14)	1.70 (1.56, 1.84)
1 severe	2.48 (2.29, 2.68)	2.66 (2.43, 2.92)
1 severe	2.27 (1.96, 2.62)	3.86 (3.25, 4.58)
≥3 severe	2.15 (1.71, 2.69)	5.35 (4.33, 6.61)

CI = confidence interval; EOS = eosinophils; IRR = incidence rate ratio; ref = reference
Source: Whittaker et al. 2022(26)

Table 47. Reference rates for moderate and severe exacerbations by GOLD severity (patients with no prior exacerbation)

GOLD Severity	Reference Rate	
	Moderate Exacerbation	Severe Exacerbation
Mild COPD	0.5	0.1
Moderate COPD	0.61	0.11
Severe COPD	1.02	0.2
Very Severe COPD	0.82	0.34

COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease
Source: Wallace et al. 2019(208) and Whittaker et al. 2022(26)

In the base case, treatment-specific exacerbation transitions are based on the specified exacerbation rate at baseline (Section B.3.3.3) and the adjusted incidence rate ratios from Whittaker et al. 2022 by number and severity of exacerbations that occurred within a prior year. Separate inputs have been generated for background therapy (Table 48) and dupilumab (Table 49). Treatment-specific exacerbation rates are applied throughout the time horizon as long as the patients are on treatment, i.e., there is no maximum treatment effect period applied to exacerbation rates.

Table 48. Transition probabilities of background therapy (base case)

From state		Exacerbation event in a cycle (%)			
COPD state	**Exacerbation state**	**# of recent exacerbations**	**No exacerbation**	**≥1 moderate exacerbation**	**≥1 severe exacerbation**
Mild COPD	No exacerbation	0	51	39	10
	Moderate exacerbation	1	30	59	11
		2	17	70	13
		3+	0	84	16
	Severe exacerbation	1	6	71	23
		2	0	68	32
		3+	0	59	41
Moderate COPD	No exacerbation	0	44	46	10
	Moderate exacerbation	1	21	66	12
		2	8	77	14
		3+	0	83	17
	Severe exacerbation	1	0	75	25
		2	0	65	35
		3+	0	56	44
Severe COPD	No exacerbation	0	18	64	18
	Moderate exacerbation	1	0	79	21
		2	0	76	24
		3+	0	71	29
	Severe exacerbation	1	0	59	41
		2	0	46	54
		3+	0	34	66
	No exacerbation	0	15	56	29
	Moderate exacerbation	1	0	66	34

From state		Exacerbation event in a cycle (%)			
COPD state	**Exacerbation state**	**# of recent exacerbations**	**No exacerbation**	**≥1 moderate exacerbation**	**≥1 severe exacerbation**
Very Severe COPD		2	0	63	37
		3+	0	56	44
	Severe exacerbation	1	0	40	60
		2	0	27	73
		3+	0	16	84

COPD = chronic obstructive pulmonary disease

Table 49. Transition probabilities of dupilumab + background therapy (reference rate vs background therapy; base case)

From state		Exacerbation event in a cycle (%)			
COPD state	**Exacerbation state**	**# of recent exacerbations**	**No exacerbation**	**≥1 moderate exacerbation**	**≥1 severe exacerbation**
Mild COPD	No exacerbation	0	[redacted]	[redacted]	[redacted]
	Moderate exacerbation	1	[redacted]	[redacted]	[redacted]
		2	[redacted]	[redacted]	[redacted]
		3+	[redacted]	[redacted]	[redacted]
	Severe exacerbation	1	[redacted]	[redacted]	[redacted]
		2	[redacted]	[redacted]	[redacted]
		3+	[redacted]	[redacted]	[redacted]
Moderate COPD	No exacerbation	0	[redacted]	[redacted]	[redacted]
	Moderate exacerbation	1	[redacted]	[redacted]	[redacted]
		2	[redacted]	[redacted]	[redacted]
		3+	[redacted]	[redacted]	[redacted]
	Severe exacerbation	1	[redacted]	[redacted]	[redacted]
		2	[redacted]	[redacted]	[redacted]
		3+	[redacted]	[redacted]	[redacted]
Severe COPD	No exacerbation	0	[redacted]	[redacted]	[redacted]
	Moderate exacerbation	1	[redacted]	[redacted]	[redacted]
		2	[redacted]	[redacted]	[redacted]
		3+	[redacted]	[redacted]	[redacted]
	Severe exacerbation	1	[redacted]	[redacted]	[redacted]
		2	[redacted]	[redacted]	[redacted]
		3+	[redacted]	[redacted]	[redacted]
Very Severe COPD	No exacerbation	0	[redacted]	[redacted]	[redacted]
	Moderate exacerbation	1	[redacted]	[redacted]	[redacted]
		2	[redacted]	[redacted]	[redacted]
		3+	[redacted]	[redacted]	[redacted]
	Severe exacerbation	1	[redacted]	[redacted]	[redacted]
		2	[redacted]	[redacted]	[redacted]
		3+	[redacted]	[redacted]	[redacted]

COPD = chronic obstructive pulmonary disease
Note: Percentages of exacerbation event in a cycle may not sum up to 100% due to rounding.

Scenario analyses have been conducted to explore the impact of using different methods to derive transition probabilities, including using transition probabilities derived from the trials. Details of these scenario analyses are provided in Appendix N.

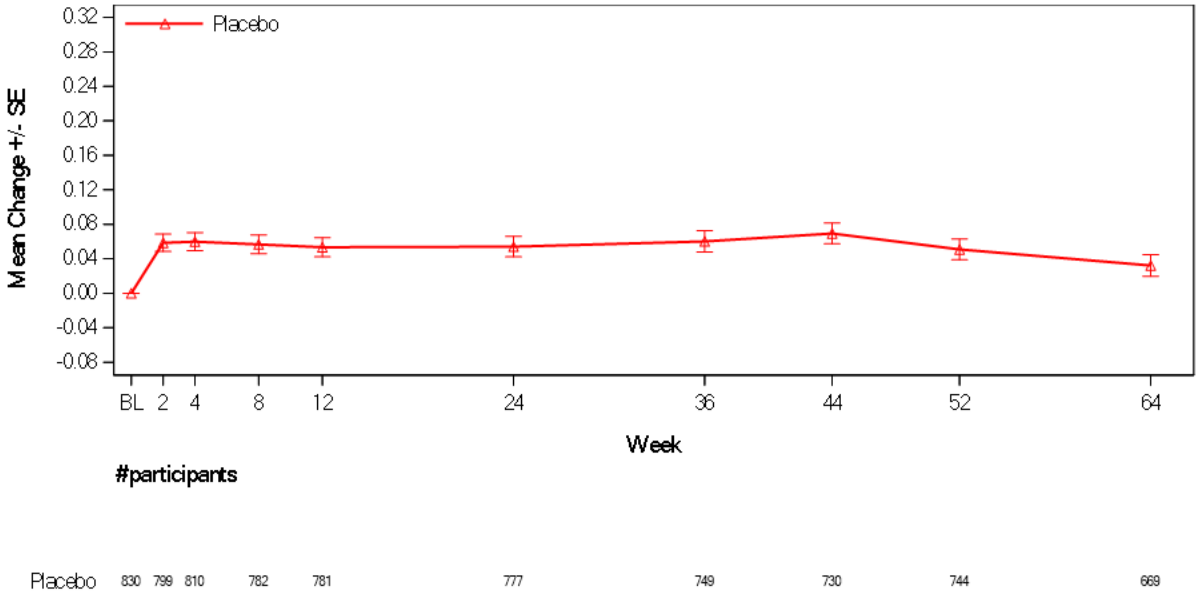
B.3.3.6. Transition probabilities across COPD stage

B.3.3.6.1. Within FEV_1 treatment effect period

Lung function measured by FEV_1 predicted is known to decline as people age and for patients with COPD this decline is more rapid (Section B.1.3.1.3).(3, 27, 31) The treatment period in the BOREAS and NOTUS trials was 52 weeks during which time an improvement in FEV_1 was observed but it is not clear for how long this lung function benefit is maintained in the longer term. The model allows for the duration of sustained FEV_1 benefit to vary by treatment arm after the trial period. Since the trial data shows that improvement in lung function is observed within 2 weeks following the initiation of dupilumab or background therapy and is sustained through Week 52, we have explored the impact of maintaining this plateau for different periods. This is the 'FEV_1 treatment effect' period (i.e., there are no transitions across COPD stage).

The post-study observation period extended to 64 weeks during which FEV_1 was collected. Figure 26 shows that immediately following the study end, FEV_1 began to decline for the patients treated with background therapy alone. This suggests that there should be no FEV_1 treatment effect period applied for background therapy in the economic model (i.e., the treatment effect for background therapy alone will wane immediately after the end of the 52-week period).

Figure 26. Mean change from baseline in pre-bronchodilator FEV_1 (L) by visit - Pooled ITT population with an opportunity to reach Week 52.



BD = bronchodilator; BL = baseline; FEV_1 = forced expiratory volume in 1 second; ITT = intention-to-treat; LS = least squares; q2w = every two weeks; SE = standard error
Source: Sanofi 2023 [Data on file] Pooled analysis summary of clinical efficacy(174)

At study end (Week 52) dupilumab was withdrawn from patients treated with dupilumab and so it is not informative to consider the period Week 52-64 to assess the FEV_1 treatment effect for dupilumab.

However, evidence from the open-label extension study TRAVERSE, in moderate-to-severe asthma demonstrated a sustained FEV_1 treatment effect of up to 148 weeks (52 weeks for the parent studies + 96 week extension) for dupilumab.(209) TRAVERSE was an open-label extension study involving 362 hospitals and clinical centres across 27 countries that assessed the safety and efficacy of dupilumab 300 mg every 2 weeks for up to 96 weeks in adults and adolescents (aged 12–84 years) with moderate-to-severe or oral-corticosteroid-dependent severe asthma who had completed a previous dupilumab asthma study (phase 2A EXPEDITION, phase 2B DRI [P2b], phase 3 QUEST, or VENTURE).(209-213) The primary endpoint was the number and percentage of patients with any treatment emergent adverse events (TEAE); secondary endpoints included the annualised exacerbation rate over the treatment period and the change from parent study baseline in pre-bronchodilator FEV_1 and anti-drug antibodies (ADAs). Efficacy results observed in TRAVERSE were consistent with the results of parent studies. In patients who were not dependent on OCS, the annualised exacerbation rate remained low (0.277 to 0.327) regardless of parent study and treatment group; improvements in pre-bronchodilator FEV_1 were also sustained through to end of treatment (Week 148).

The TRAVERSE asthma study included patients with type 2 inflammation as do the BOREAS and NOTUS trials for COPD. The mode of action of dupilumab on the IL4/13 receptors is common to both these patient groups. Taking these results into account and considering the immediate decline of FEV_1 observed in the period directly after the study end for patients treated with background therapy only (Figure 26) our base case assumes that patients on dupilumab + background therapy experience an FEV_1 treatment effect period of 2 years beyond the trial, whereas the treatment effect for background therapy alone is assumed to wane immediately after the end of the 52-week period.

In addition, we undertook an SEE exercise with seven clinicians with experience of managing COPD in clinical practice from different centres in England to consolidate their opinions on how long the trial based FEV_1 benefit might be maintained outside the confines of the studies before natural FEV_1 decline might be expected to resume. The aggregated responses from the experts suggested that the time to loss of maintenance of FEV_1 for the patients on background therapy alone is likely to be short (2.85 months in round 1 and 2.96 months in round 2), whereas for patients who continue dupilumab the time to decline is expected to be much longer (9.06 months in round one and 6.60 months in round 2). More information on the SEE can be found in Appendix P.

Taking this opinion into account and the immediate decline of FEV_1 observed in the period directly after the study end for patients treated with background therapy only (Figure 26), we also included a scenario where patients on dupilumab + background therapy only experience an FEV_1 treatment effect period of 1 year beyond the trial (SEE result rounded to 1 year due to the cycle length in the

model), and the treatment effect for background therapy alone is again assumed to wane immediately after the end of the 52-week period.

B.3.3.6.2. Beyond the FEV_1 treatment effect period

Beyond the FEV_1 treatment effect period, FEV_1 is assumed to decline at an accelerated rate for COPD patients (compared to the age-matched population). The COPD health states are defined by FEV_1 and so transitions between them are informed by the annual probabilities reported by Fenwick et al. 2021,(192) which were based on statistical equations for FEV_1 decline over time using data from the 3-year Towards a Revolution in COPD Health (TORCH) study.

In Fenwick et al. 2021, the slope coefficient (-40.9) refers to an annual decline of 40.9 mL in FEV_1 for individuals with no recent history of an exacerbation.(192) This was based on a regression equation fit to the data from the TORCH study.(192) The coefficient for recent exacerbation history (-30.6) reflects the additional decline in FEV_1 mL for those individuals with a recent exacerbation (within the last year).(192) These values were used to calculate the time taken for a "typical" patient in each COPD severity category to cross the threshold to the next severity category, as outlined in the 2010 UK NCGC guideline for management of COPD in adults.(214) The typical patient was defined by the characteristics of the trial population and assumed to currently be at the mid-point of the severity category (i.e., 65% FEV_1 predicted for moderate COPD and 40% FEV_1 pred for severe COPD).(192) The FEV_1 predicted for the typical patient at the mid-point of each severity category was calculated from the ERS equations using height and age (Table 6 in Quanjer et al. 1993).(215) The time in years until the mid-point of the next severity category is reached was derived with the application of the annual reduction.(192) The estimated time was then converted to a transition probability assuming an exponential distribution over time. The estimates provide the transition probabilities associated with COPD severity and exacerbation history.

The presence of Type 2 inflammation in COPD patients, indicated by elevated blood EOS, is associated with further acceleration of lung function decline.(41) Recent findings from the CanCOLD study found that an EOS count ≥300 cells/μL was a significant and independent risk factor for accelerated lung function decline in COPD (Section B.1.3.1.3).(41) In a sensitivity analysis, the CanCOLD study investigated annual rates of FEV_1 decline in a cohort of COPD patients with comorbid asthma excluded.(41) We have deemed this the most appropriate and conservative data to inform annual lung function decline in patients best fitting the BOREAS/NOTUS criteria. The study categorised these COPD patients into three groups based on their blood EOS counts: those with EOS <150 cells/μL, those with EOS 150 to 299 cells/μL and those with EOS ≥300 cells/μL.(41) The annual decline in FEV_1 was recorded for each group:(41)

- EOS ≥150 cells/μL: 23.81 mL/year (n=182)
- EOS ≥150 to <300 cells/μL: 38.71 mL/year (n=168)
- EOS ≥300 cells/μL: 58.51 mL/year (n=116)

To obtain the overall rate for the full cohort (N=466), we calculated a weighted average of these rates of decline by multiplying the rate for each group by the proportion of patients in that group, and summing the results:

- Overall rate of decline: (182/466*23.81)+(168/466*38.71)+(116/466*58.51)=38.47 mL/year

To quantify the impact of high EOS counts on lung function decline, the rate of decline for the EOS ≥300 cells/μL group was compared to the overall cohort rate:

- Ratio: 58.51/38.47=1.52

This ratio of 1.52 indicates that patients with EOS ≥300 cells/μL experienced a 52% higher rate of FEV_1 decline compared to the overall cohort. We have applied this modifier as well as the average patient age and height at baseline from the pooled BOREAS and NOTUS trials to the transition probabilities reported by Fenwick et al. 2021 (Table 50) to derive transition probabilities that are more appropriate for use in patients with Type 2 inflammation. The transition probabilities are applied equally to both treatment arms.

Table 50. Annual transition probabilities between COPD stage beyond treatment effect period

Transition between COPD stage	Exacerbation status	Annual transition probabilities as reported by Fenwick et al. 2021(192)	Annual transition probabilities with Type 2 modifier derived from Tan et al. 2021 applied(41)
Mild COPD -> Moderate COPD	No exacerbation	4.1	7.83
	Moderate exacerbation	8.8	14.28
	Severe exacerbation	8.8	14.28
Moderate COPD -> Severe COPD	No exacerbation	4.1	7.83
	Moderate exacerbation	8.8	14.28
	Severe exacerbation	8.8	14.28
Severe COPD -> Very Severe COPD	No exacerbation	7.0	11.84
	Moderate exacerbation	14.3	24.21
	Severe exacerbation	14.3	24.21

COPD = chronic obstructive pulmonary disease
Due to lack of transition probabilities from mild COPD to moderate COPD, inputs for transition from moderate COPD to severe COPD are applied. Transition probabilities from the source are not differentiated by exacerbation severity (i.e., moderate or severe), therefore, the probabilities with recent exacerbation history are applied regardless of exacerbation severity.
Source: Fenwick et al. 2021(192) and Tan et al. 2021(41)

B.3.3.7. Discontinuation of dupilumab within and beyond the trial period

In addition to the response assessment described in Section B.3.3.2, treatment discontinuation due to other causes is also considered in the model. Since dupilumab is used as add-on therapy to background therapy, treatment discontinuation in the model is only considered for dupilumab. Patients on background therapy are assumed to remain on the same treatment regimen throughout the time horizon.

Based on the pooled trial analysis, 90.7% of the patients in the dupilumab group completed the 52-week trial period (Section B.2.3.2.3).(174) Therefore, in the base case, a treatment discontinuation rate of 9.3% is applied as one-off at 52 weeks represented by the decision tree component of the model.

There are no direct data from the dupilumab COPD studies upon which to base longer term discontinuation. Therefore, we have considered several sources described below with a range of 15% to 25.8%:

Base case setting

- UK data on the real world persistence rate for dupilumab in asthma are available for three full years from Sanofi homecare in 1,488 active patients. The weighted average persistence for all patients with 12 months of treatment is [redacted]%, [redacted]% at 24 months and [redacted]% at 3 years.(216) Assuming that the discontinuation rate for dupilumab in the treatment of moderate to severe asthma can stand as a proxy, these data suggest that ~15% may be a reasonable rate to include in the model. However, this may be an underestimate for COPD patients treated with dupilumab in the real world as it is known that persistence to inhaled therapies is generally less than 50% in this patient group.(217-219)
- Feedback on the likely rate of discontinuation in the post-trial setting was obtained from the advisory board conducted by Sanofi in July 2024 with five respiratory clinicians and two health economists. The experts estimated that the annual treatment discontinuation rate for biologics is 15% to 20% in the real-world setting and that this would not be unreasonable for dupilumab in COPD.(167) Note the asthma discontinuation rates were not shown to the experts.
- We have adopted the lower end of this range 15% in the base case and tested higher values (including those below) in sensitivity analysis.

Sensitivity analysis

- No biologics beyond dupilumab have received marketing authorisation and there are no real-world data upon which to base discontinuation of biologics in COPD more generally. A study by Mansur et al. 2022 evaluated the clinical outcomes of 898 patients registered in the UK Severe Asthma Registry (UKSAR) treated with biologics (median follow-up: 398 days).(220) Most patients (n=697; 77.6%) had a good clinical response and continued their initial treatment.(220) Therefore, although these data are from the asthma therapy area they might be considered a proxy for COPD and a treatment discontinuation rate of 22.4% is tested in sensitivity analysis.
- In an alternative setting during structured expert elicitation (Appendix P), the consensus was that real world discontinuation with dupilumab in the post-trial period would be 25.8%. This is therefore tested in a scenario analysis.

B.3.3.8. Mortality inputs

COPD patients experience an increased risk of death compared with the general population and it is estimated that ~22,000 people die each year in England of COPD, many of which are premature deaths (Section B.1.3.1.3).(16, 58, 221) The model is designed to capture the excess mortality risk associated with COPD as accurately as possible. Based on the review of prior economic models (Section B.3.1),(192, 193) the excess mortality due to COPD has been linked to both COPD stage and to exacerbations. The model aims to capture the increased mortality due to GOLD severity and exacerbations separately via a standardised mortality ratio (SMR) vs. the general population mortality derived from UK lifetables. A fixed probability of 15.6%, derived from Hoogendorn 2011, is applied to patients who experience a severe exacerbation. It is assumed that patients who experience moderate exacerbation do not experience any excess mortality.(222)

B.3.3.8.1. Adjusted general population mortality

The general population mortality directly derived from the UK lifetables(223) already includes COPD-related deaths. To ensure that the effect of mortality is not overstated/double-counted, the proportion of COPD-related deaths is removed from the lifetables by subtracting the death events associated with ICD-10 codes J40-J44 (COPD-related deaths).

B.3.3.8.2. Excess mortality associated with COPD stage

The excess mortality associated with each COPD stage is derived from Whittaker et al. 2024.(30) This study provides SMRs stratified by GOLD severity, utilising data from the CPRD, which was linked to HES and death certificate data for 339,647 individuals in England with COPD who were alive between January 2010 and January 2020.(30) The SMR values used in the base case analysis were based on all-cause mortality hazard ratios adjusted for baseline characteristics, including history of prior exacerbations, airflow obstruction, age, gender, smoking status, BMI, MRC dyspnoea grades, gastroesophageal reflux disorder, heart failure, myocardial infarction, stroke, depression, anxiety, lung cancer, hypertension, diabetes and current asthma .(30) The specific SMR values applied in the base case of the model from Whittaker et al. 2024 are detailed in Table 51.(30)

Table 51. Excess mortality due to GOLD severity grade

COPD GOLD severity	SMR	Lower 95% CI	Upper 95% CI
Mild COPD†	1.0	1.0	1.0
Moderate COPD	1.45	1.42	1.48
Severe COPD	2.33	2.28	2.39
Very Severe COPD	4.1	3.95	4.25

† Mild COPD was considered the reference subgroup and is assumed to be the same as general population
CI = confidence interval; COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; SMR = standardised mortality ratio
Source: Whittaker 2024(30)

Scenario analyses (see section B.3.11.3) have been conducted using the SMRs by GOLD severity reported by Leivseth et al. 2013 (described in Section B.1.3.1.3) and by Shavelle et al. 2009.(61, 66)

B.3.3.8.3. Excess mortality associated with exacerbation

In addition to the excess mortality associated with COPD, a recent severe exacerbation is associated with an increased risk of mortality (Section B.1.3.1.3) and therefore an additional case-fatality rate per severe exacerbation has been incorporated in the model. This parameter is informed by Hoogendoorn et al. 2011(222), who derived the probability of mortality following a severe exacerbation from six studies(224-229) that reported survival rates for at least 1.5 years post-exacerbation. The application *of* a case-fatality rate exclusively for severe exacerbations is a conservative approach, as it does not consider the excess mortality following moderate exacerbations or the cumulative effect of prior moderate exacerbations. Rothnie et al. 2018 demonstrated in a UK CPRD database study that an increased frequency of moderate exacerbations is associated with higher all-cause mortality in a generalisable population of COPD patients.(230) However, the model focuses on the excess mortality of a severe exacerbation due to the high burden of disease associated with such events. The case-fatality rate per severe exacerbation obtained from the Hoogendoorn et al. 2011 meta-analysis is provided in Table 52.(222)

Table 52. Case-fatality rate per severe exacerbation

COPD exacerbation	Mean case-fatality rate (%)	Lower 95% CI	Upper 95% CI
Severe exacerbation	15.6	10.9	20.3

CI = confidence interval; COPD = chronic obstructive pulmonary disease
Source: Hoogendoorn 2011(222)

B.3.4. Measurement and valuation of health effects

In the model, the impact of treatment on patient HRQoL is accounted for by the following:

- HRQoL measurements tied to the COPD states
- Disutilities associated with exacerbations
- Disutilities associated with adverse events and CV events

B.3.4.1. Health-related quality of life data from clinical trials

The impact of dupilumab on HRQoL was captured in the BOREAS and NOTUS trials.(168, 169) No other trials are available reporting data on the impact of dupilumab on HRQoL in patients with uncontrolled COPD.

In both BOREAS and NOTUS, HRQoL was extensively evaluated using SGRQ at baseline and during follow-up (at Weeks 4, 12, 24, 36 and 52).(168-171) In NOTUS, EQ-5D-5L was only collected at baseline and during follow-up at Weeks 24 and 52, while in BOREAS, EQ-5D-5L was only collected at baseline.(170, 171)

The severity of respiratory symptoms was also assessed in both trials using the 11-item Evaluating Respiratory Symptoms in COPD (E-RS: COPD) scale, with data collected at baseline and during

follow-up (at Weeks 1, 2, 3, 4, 8, 12, 24, 36, 44 and 52).(170, 171) Results for all PRO measures are reported in Section B.2.

B.3.4.2. Mapping

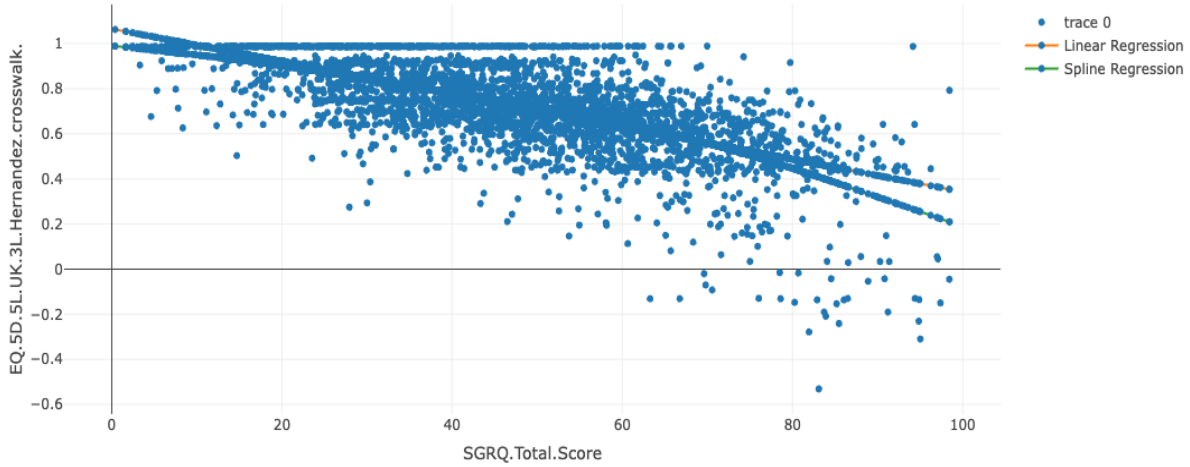
A targeted search was performed to identify published mapping algorithms that could be used to map SGRQ to EQ-5D. Among the available literature, only three studies were identified: Starkie et al. 2011,(187) Stahl et al. 2005,(231) and Freemantle et al. 2016.(232) However, further analysis revealed limitations in all the published algorithms, and their results did not fully align with the baseline EQ-5D-5L data from the BOREAS and NOTUS studies. Consequently, we developed our own mapping algorithm using data directly from the studies to derive utilities from SGRQ.

The analysis included the pooled data from the two Phase 3 studies NOTUS and BOREAS, encompassing visits where both SGRQ and EQ-5D-5L were assessed. After excluding missing data, the final dataset for mapping consisted of 3,011 observations.

- Notably, missing data occurred only when all items of the SGRQ or all dimensions of the EQ-5D-5L were absent, and no imputation was performed when scoring SGRQ Total or EQ-5D-5L Utility using tariffs.
- The distribution of SGRQ and EQ-5D-5L measures was highly similar between the two studies, and their relationship remained stable over time. As a result, data from both studies and all visits were pooled for analysis.

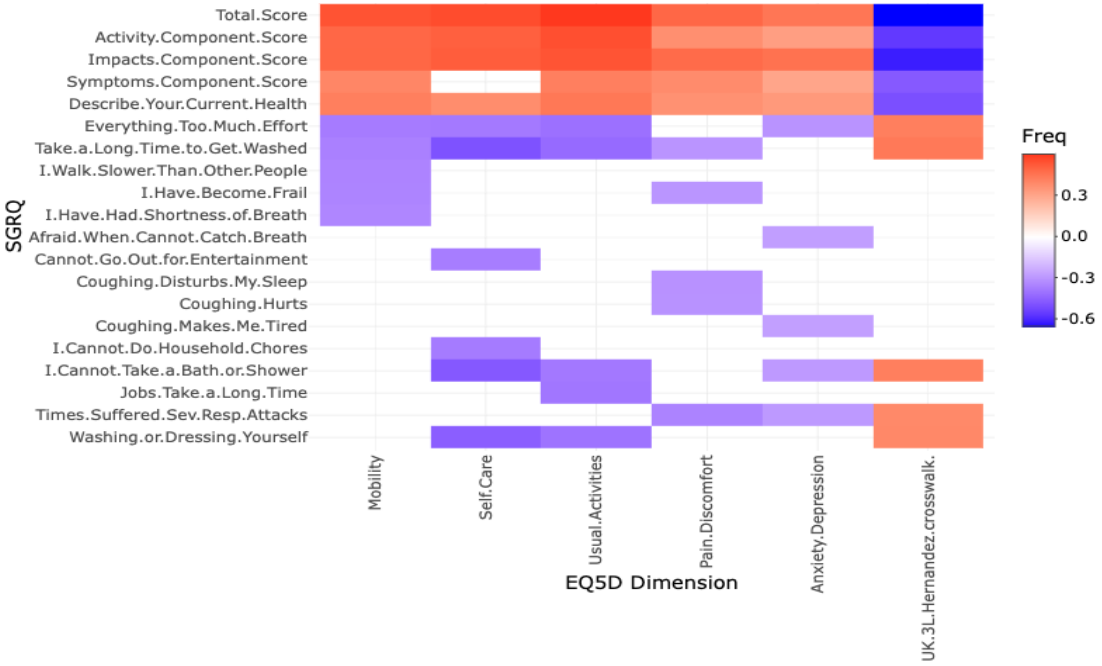
Figure 27 illustrates the positive correlation between EQ-5D-5L responses and SGRQ total score, while Figure 28 identifies the SGRQ items that most closely correlate with EQ-5D-5L dimensions and utility.

Figure 27. Scatterplot of SGRQ total score vs EQ-5D-5L Hernandez cross-walked to 3L



EQ-5D-5L = EuroQoL 5-Dimension 5-Level; SGRQ = St. George's Respiratory Questionnaire

Figure 28. Top items of SGRQ most correlated with EQ-5D-5L dimensions and utility



EQ-5D-5L = EuroQoL 5-Dimension 5-Level; SGRQ = St. George's Respiratory Questionnaire

In order to develop the mapping algorithm, two different model types were evaluated:

- Linear Regression
- Two-Part Model

The choice of model was guided by multiple performance metrics:

- Prediction Accuracy: Evaluated using mean prediction error (MAE, MRSE, PME, R^2).
- CDF Analysis: Comparison of cumulative distribution functions (CDF) of observed data versus simulations (using visualisation plots).
- Bias Analysis: Visual comparison of prediction bias (mean differences) between observed and predicted values, stratified by predictor classes.
- Change From Baseline (CFB): Given the longitudinal nature of the data, CFB analysis was performed. Lower differences in mean (std) between observed and predicted CFB values were preferred.

The linear model was the best fit according to the criteria above. The developed mapping models were created using an out-of-sample approach, with a 70/30 split between training and testing datasets (Table 53): Training data: n=2,107 (70%) and Testing data: n=904 (30%). Sensitivity analyses with different training percentages were also performed.

Table 53. Utility linear regression model values – using 70% training (final model)

Covariates	Estimate	Std. Error	T value	Pr(>|t|)
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
SGRQ total score 10	[redacted]	[redacted]	[redacted]	[redacted]
SGRQ total score2 100	[redacted]	[redacted]	[redacted]	[redacted]

Covariates	Estimate	Std. Error	T value	Pr(>|t|)
Moderate GOLD (Grade 2)	[redacted]	[redacted]	[redacted]	[redacted]
Severe GOLD (Grade 3)	[redacted]	[redacted]	[redacted]	[redacted]
Very severe GOLD (Grade 4)	[redacted]	[redacted]	[redacted]	[redacted]
Gender = male	[redacted]	[redacted]	[redacted]	[redacted]
Age 10	[redacted]	[redacted]	[redacted]	[redacted]
Age2 100	[redacted]	[redacted]	[redacted]	[redacted]

GOLD = Global initiative for chronic obstructive pulmonary disease; Pr(>|t|) = P-value (Probability value) for the T Statistic; SGRQ = St. George's Respiratory Questionnaire; Std. error = standard error; T value = test statistic

For this analysis, EQ-5D-5L data was converted to utilities using the UK crosswalk tariff developed by Hernández Alava.(233) Then mapping between SGRQ from the pooled BOREAS and NOTUS ITT population and the UK utility tariff was performed.

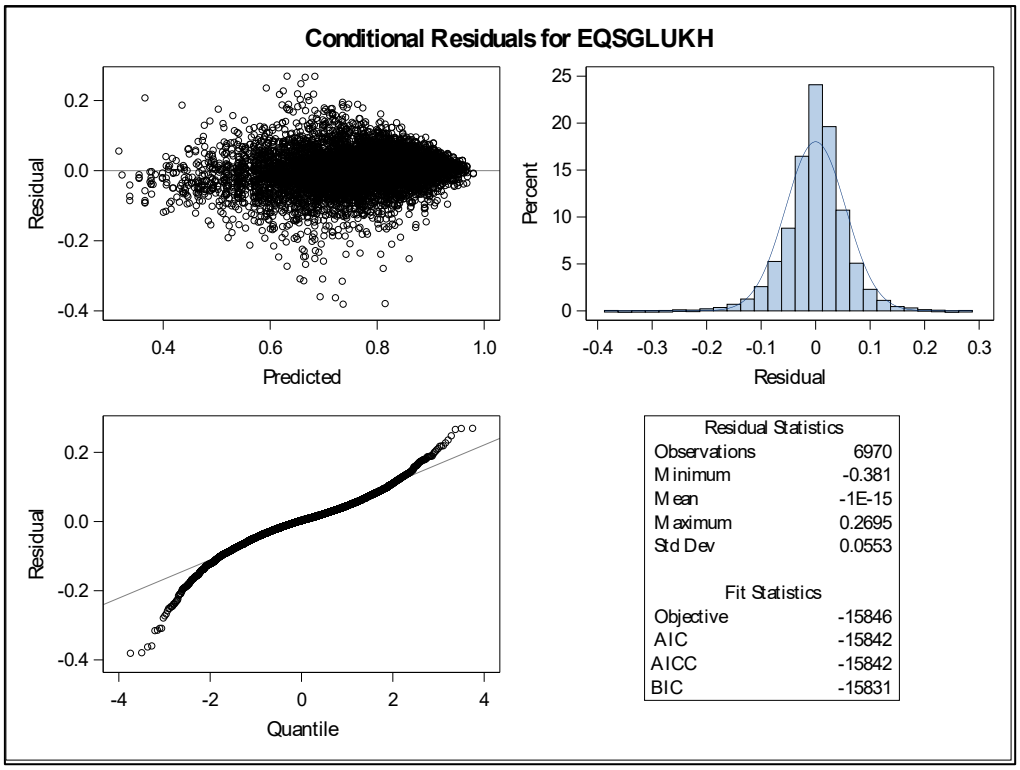
A linear regression analysis was performed to convert the utility values to EQ-5D-3L, using the UK Crosswalk tariffs. Utility scores up to Week 52 were incorporated, utilising all observed data points. Table 54 presents the parameter estimates and Figure 29 displays the conditional residuals from the linear regression model.

Table 54. Pooled ITT linear regression of utility based on SGRQ (UK crosswalk tariffs, Hernandez 2020) - Parameter estimates

Parameter	Estimate (SE)	[95% CI]	p-value
Intercept	[redacted]	[redacted]	<.0001
Treatment = Dupilumab 300mg q2w	[redacted]	[redacted]	0.3426
Study	[redacted]	[redacted]	0.0718
Age	[redacted]	[redacted]	0.1115
Gender = Male	[redacted]	[redacted]	0.2493
SGRQ-based utility at baseline	[redacted]	[redacted]	<.0001
Health State - severity of airflow obstruction			
Moderate FEV_1	[redacted]	[redacted]	<.0001
Severe FEV_1	[redacted]	[redacted]	<.0001
Very Severe FEV_1	[redacted]	[redacted]	<.0001
Health State - exacerbation risk			
Moderate	[redacted]	[redacted]	<.0001
Severe	[redacted]	[redacted]	<.0001
Treatment x Health State - severity of airflow obstruction			
Dupilumab 300mg q2w x Moderate FEV_1	[redacted]	[redacted]	0.2153
Dupilumab 300mg q2w x Severe FEV_1	[redacted]	[redacted]	0.4131
Dupilumab 300mg q2w x Very Severe FEV_1	[redacted]	[redacted]	0.7859

CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; mg = milligrams; P-value = Probability value for the T Statistic; q2w = administered every two weeks; SE = standard error; SGRQ = St. George's Respiratory Questionnaire; UK = United Kingdom

Figure 29. Pooled ITT mixed-model diagnostics (UK crosswalk tariffs, Hernandez 2020)



AIC = Akaike information criterion; AICC = Akaike information criterion corrected for sample size; BIC = Bayesian information criterion; EQ5DUKH = regression model using algorithm by Hernández Alava (2020)

Table 55 presents the LS means for each health state, adjusted for covariates in the model. These LS means represent the utility values used in the base case analysis.

Table 55. Pooled ITT linear regression of utility based on SGRQ (UK crosswalk tariffs, Hernandez 2020) – LS means by health state

Health state	LS Mean (SE)	[95% CI]	p-value
Placebo x Mild FEV_1	[redacted]	[redacted]	<.0001
Placebo x Moderate FEV_1	[redacted]	[redacted]	<.0001
Placebo x Severe FEV_1	[redacted]	[redacted]	<.0001
Placebo x Very Severe FEV_1	[redacted]	[redacted]	<.0001
Dupilumab x Mild FEV_1	[redacted]	[redacted]	<.0001
Dupilumab x Moderate FEV_1	[redacted]	[redacted]	<.0001
Dupilumab x Severe FEV_1	[redacted]	[redacted]	<.0001
Dupilumab x Very Severe FEV_1	[redacted]	[redacted]	<.0001
Exacerbations			
No exacerbation	[redacted]	[redacted]	<.0001
Moderate exacerbation	[redacted]	[redacted]	<.0001
Severe exacerbation	[redacted]	[redacted]	<.0001

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; ITT = intent-to-treat; LS = least squares; SGRQ = St. George's Respiratory Questionnaire; UK = United Kingdom

Further details on the mapping exercise are provided in Appendix Q and the results which are used in the base case are presented in Section B.3.4.4.

B.3.4.3. Health-related quality of life studies

An SLR was conducted, with a cut-off date of 19 August 2024, to identify studies reporting health utility values and HRQoL measures in patients with uncontrolled COPD (Appendix H). In total, 4,370 records were identified by the SLR, including 3,238 records via Embase, 1,755 records via MEDLINE, 1,248 records via the Cochrane Central Register of Controlled Trials (CENTRAL) and 49 records via the CDSR. No relevant publications were identified through grey literature searches. Following title/abstract and full-text screening, a total of eleven publications, pertaining to ten studies, were included in the SLR (Table 56). Across the ten studies, eight had observational study designs. Two studies used populations from RCTs (the RESTORE study and the ETHOS study) as the basis for further analyses and were the only studies in which interventions were evaluated (neither included dupilumab). Three studies evaluated multinational populations, while two studies were identified from Spain, two from the United States (US) and the remaining studies were from Austria, Canada, and Germany.

None of the studies identified in the SLR reported UK data on the utilities associated with each COPD state.

Table 56. Utilities studies in patients with moderate to severe COPD identified by the SLR

Author	Year	Study design	Country	Title
Calverley	2022	Retrospective analysis of RCT	Multinational	The Effect of Maintenance Treatment with Erdosteine on Exacerbation Treatment and Health Status in Patients with COPD: A Post-Hoc Analysis of the RESTORE Dataset.
Charbonnier	2019	Cross-sectional	US	Airway wall thickening on CT: Relation to smoking status and severity of COPD.
Cherian	2020	Prospective	Canada	Dyspnoea and symptom burden in mild-moderate COPD: the Canadian Cohort Obstructive Lung Disease Study.
Choate	2023	Cross-sectional	US	Characteristics Associated With SGRQ in Alpha-1 Antitrypsin Deficiency Associated Lung Disease: A Cross-sectional Analysis.
Gainza-Miranda	2019	Prospective	Spain	Breaking Barriers: Prospective Study of a Cohort of Advanced Chronic Obstructive Pulmonary Disease Patients To Describe Their Survival and End-of-Life Palliative Care Requirements.
Horner	2020	Cross-sectional	Austria	Quality of Life and Limitations in Daily Life of Stable COPD Outpatients in a Real-World Setting in Austria - Results from the CLARA Project.
Jackson	2024	Longitudinal mixed model using data from the ETHOS trial	Multinational	1. The association between health-related quality of life and COPD exacerbations measured by EQ-5D-5L in the ETHOS trial. 2. Associations between the EQ-5D-5L and exacerbations of chronic obstructive pulmonary disease in the ETHOS trial.
Meeraus	2021	Prospective	Multinational	Predicting Re-Exacerbation Timing and Understanding Prolonged Exacerbations: An Analysis of Patients with COPD in the ECLIPSE Cohort.

Author	Year	Study design	Country	Title
Merino	2019	Cross-sectional	Spain	Collaborative Working Group E-E. Health-related quality of life of patients diagnosed with COPD in Extremadura, Spain: results from an observational study.
Song	2020	Retrospective	Germany	Quantitative CT Analysis in Patients with Pulmonary Emphysema: Do Calculated Differences Between Full Inspiration and Expiration Correlate with Lung Function?

COPD = chronic obstructive pulmonary disease; CT = computed tomography; EQ-5D-5L = EuroQoL 5-Dimension 5-Level; RCT = randomised controlled trial; SGRQ = St. George's Respiratory Questionnaire; SLR = systematic literature review; US = United States

B.3.4.4. Health state utilities

In the BOREAS trial, the EQ-5D-5L questionnaire was collected solely at baseline. Conversely, in the NOTUS trial, the EQ-5D-5L was collected at baseline as well as during follow-up assessments at Weeks 24 and 52. Due to the inconsistent collection of EQ-5D data across the trials and to make full use of the available SGRQ data collected at all time points in both studies. The differing utility values assigned to dupilumab + background therapy and background therapy reflect the improved quality of life reported by patients in both trials, as indicated by the mapped SGRQ results, which is used in our base case. The mapped SGRQ utilities exercise is described in Section B.3.4.2 and Appendix Q. The mapped utilities according to GOLD stage are tabulated in Table 57.

Table 57. Base case: mapped SGRQ to EQ-5D-3L health state utilities according to GOLD stage

Predictor	Dupilumab + Background Therapy	SE	Background Therapy	SE
Mild COPD	[redacted]	0.008	[redacted]	0.008
Moderate COPD	[redacted]	0.005	[redacted]	0.005
Severe COPD	[redacted]	0.005	[redacted]	0.005
Very severe COPD	[redacted]	0.009	[redacted]	0.009

COPD = chronic obstructive pulmonary disease; EQ-5D-3L = EuroQoL 5-Dimension 3-Level; SE = standard error; SGRQ = St. George's Respiratory Questionnaire

We have also provided several alternative sources for utility and a key sensitivity analysis uses the published utility values from Spencer et al. 2005(234) and Sadatsafavi et al. 2019(235) to further address the limitations posed by the trial-collected EQ-5D data. The utility values used in this sensitivity analysis are presented in Table 58.

The model adjusts the utilities based on the reference age in the trial to the starting age of the cohort based on a utility multiplier derived from HSE 2014, according to NICE best practice (Section B.3.4.7).(236)

In a sensitivity analysis, EQ-5D data directly captured in the NOTUS study are used encompassing the NOTUS EQ-5D-5L data with UK crosswalk tariff (Hernandez 2020)(233) and NOTUS mean-adjusted CFB crosswalk LS-regression (Table 58 and Appendix R).(171, 233) Note that the NOTUS data are used as this includes EQ-5D collected at baseline, Week 24 and study end whereas BOREAS only reports baseline EQ-5D. Details of the regression analysis are provided in Appendix R.

Further alternative published sources of utilities have been used to fully explore the impact of varying health state utilities associated with the severity of airflow obstruction.

Table 58. Utility measurements associated with each COPD state used in sensitivity analysis

COPD stage	Scenarios			
	Spencer et al. 2005(234), Sadatsafavi et al. 2019(235)	**Mean adjusted CFB crosswalk, LS-regression (Hernandez-NOTUS(171, 233))**	**Rutten Van Molken et al. 2006(200)**	**Borg et al. 2004(237)**
Mild COPD	0.81	Dupilumab: 0.77 Background: 0.78	0.79	0.90
Moderate COPD	0.72	Dupilumab: 0.74 Background: 0.73	0.79	0.76
Severe COPD	0.68	Dupilumab: 0.73 Background: 0.70	0.75	0.75
Very severe COPD	0.58	Dupilumab: 0.68 Background: 0.66	0.65	0.55
Reference Age	65†	65	64.5	64.3

CFB = change from baseline; COPD = chronic obstructive pulmonary disease; LS = least squares; † Assumed to be the starting age of the modelled population

For the external studies, a multiplicative age adjustment based on the general population utility (Section B.3.4.7) is used to derive the baseline utility by COPD stages. The reference age of the external studies could be derived for Borg et al. 2004(237) and Rutten Van Molken et al. 2006(200), but could not be derived reliably for Spencer et al. 2005(234), Sadatsafavi et al. 2019(235) and was assumed to be the same as the starting age of the modelled population.

B.3.4.5. Disutilities associated with exacerbations

Since exacerbation events have a profound impact on the HRQoL of patients with COPD, a disutility is applied to each exacerbation event. In the base case, utility decrements derived from the SGRQ to EQ-5D-3L mapping exercise are used (Appendix Q). It is assumed that acute disutilities associated with moderate or severe exacerbations last for 3 months, while no chronic impact (i.e., longer than 3 months) of exacerbations on utilities is included (Table 59).

In a scenario analysis, exacerbation-associated disutilities derived from the NOTUS trial are used (when the NOTUS utilities are selected to inform COPD states the model automatically applies the NOTUS disutility). In the NOTUS utility regression, exacerbations occurring within 3 months prior to the utility assessment are included as acute events. Additionally, a scenario analysis has been conducted using the QALY losses associated with exacerbations reported by Rutten van Molken et al. 2009(201) and used in the NICE NG115 COPD economic model(189) (moderate exacerbation: -0.01; severe exacerbation: -0.04).

Table 59. Summary of disutilities associated with exacerbations

Exacerbation	Acute Impact		Chronic Impact		Source
	Utility Decrement	Duration (Months)	Utility Decrement	Duration (Months)	
Base case					
Moderate exacerbation	[redacted]	3	0	12	Mapped SGRQ to EQ-5D-3L based on pooled analysis (Appendix Q)
Severe exacerbation	[redacted]	3	0	12	
Scenario analysis					
Moderate exacerbation	0.028	3	0	12	NOTUS(171)
Severe exacerbation	0.048	3	0	12	
Moderate exacerbation	0		0.01	12	Rutten van Molken et al. 2009(201)
Severe exacerbation	0		0.04	12	

EQ-5D-3L = EuroQoL 5-dimension 3-level; SGRQ = St. George's Respiratory Questionnaire

B.3.4.6. Adverse events and cardiovascular events

For each AE, the associated disutility and duration are applied to the proportion of patients who experienced an event in each cycle. However, since the AEs observed in the dupilumab studies were all considered to be mild, a simplifying approach is taken in the base case and the disutilities associated with AEs are assumed to be 0 in both arms of the model.

Given the increased risk of CV events following a COPD exacerbation,(29) the model is designed so that patients may experience CV events (myocardial infarction, unstable angina, transient ischemic attack and stroke) in each cycle. Rates for the incidence of these events are presented in Section B.2.10.1. The disutilities associated with CV events are derived from Sterne et al. 2017 (Table 60).(238)

Table 60. Disutilities associated with CV events

CV Event	Disutility	Duration	Source
Myocardial infarction	0.096	3 months	Sterne 2017(238)
Stroke	0.59	3 months	Sterne 2017(238)
Unstable angina	0.131	1 month	Assumed to be the same as transient ischemic attack
Transient ischemic attack	0.131	1 month	Sterne 2017(238)

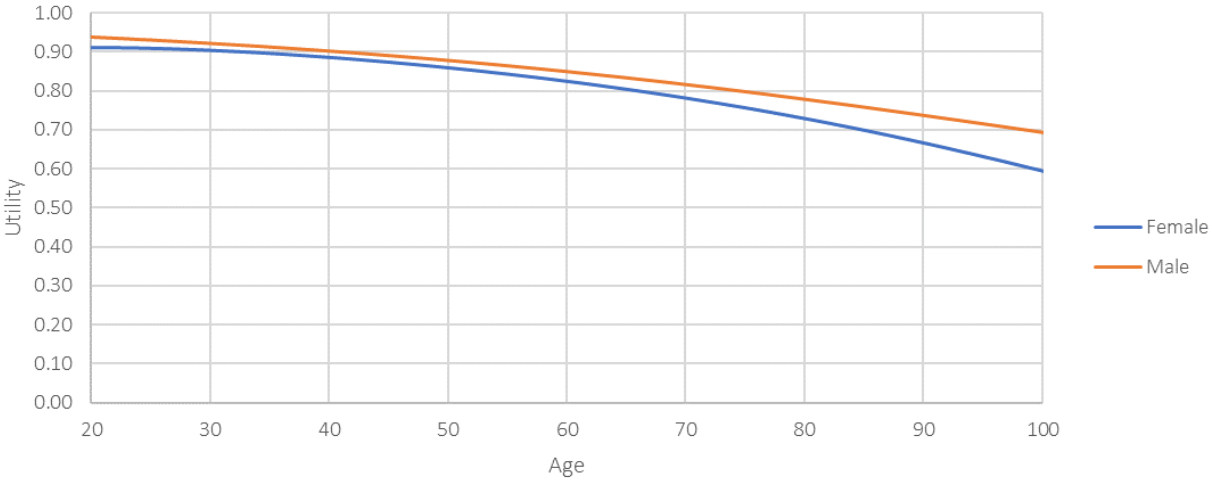
CV = cardiovascular

B.3.4.7. Decline of utility by age

Age-adjusted utility values are included in the model to account for the expected decrease over time in HRQoL associated with ageing. The utility estimates for each model cycle are adjusted based on the difference between patients' mean age during the current cycle and the mean age at baseline. The age-adjusted utilities are included using the mean EQ-5D-3L values by age estimated from the

latest available wave of the Health Survey for England (HSE) that included the EQ-5D-3L (2014; Figure 30).(236)

Figure 30. EQ-5D-3L by age and gender in the UK (HSE 2014)(236)



EQ-5D-3L = EuroQoL 5-Dimension 3-Level; HSE = Health Survey for England; UK = United Kingdom

B.3.4.8. Health-related quality of life data used in the cost-effectiveness analysis

COPD is an incurable disease associated with elevated mortality risk and major CV events due to the recurrent exacerbations that require hospitalisation. The clinical manifestations and consequences of COPD, for example disease stage progression, exacerbations, CV events and the psychological, socioeconomic and functional effects of living with the disease, have substantial negative impacts on patient HRQoL. Accordingly, patients incur greater utility loss with increasing COPD severity as well as disutilities associated with exacerbations and CV events.

The utility values used in the base case analysis are summarised in Table 61.

Table 61. Summary of utility values for the base case cost-effectiveness analysis

State	Utility/disutility value, mean (SE)						Reference in submission (section and page number)	Justification
Health states	**Dupilumab + Background Therapy**			**Background Therapy**				
	Utility	**95% CI**		**Utility**	**95% CI**			
Mild COPD	[redacted]	[redacted]		[redacted]	[redacted]		Section B.3.4.4 (p 138)	Derived from mapping of the SGRQ to EQ-5D in order to utilise all the available data from both studies.
Moderate COPD	[redacted]	[redacted]		[redacted]	[redacted]			
Severe COPD	[redacted]	[redacted]		[redacted]	[redacted]			
Very severe COPD	[redacted]	[redacted]		[redacted]	[redacted]			
Exacerbations	**Acute impact**			**Chronic impact**				
	Utility decrement	**Duration (months)**	**95% CI**	**Utility decrement**	**Duration (months)**	**95% CI**		
Moderate exacerbation	[redacted]	3	[redacted]	0	0	[0, 0]	Section B.3.4.5 (p 139)	Derived from mapping of the SGRQ to EQ-5D in order to utilise all the available data from both studies.
Severe exacerbation	[redacted]	3	[redacted]	0	0	[0, 0]		
CV events	**Utility decrement**			**Duration (months)**		**95% CI**		
Myocardial infarction	0.096 (0.1)			3 months		[0.08; 0.12]	Section B.3.4.6 (p 140)	Derived from a cost-effectiveness analysis for venous thromboembolic disease and stroke in atrial fibrillation conducted by the National Institute for Health Research Health Technology Assessment programme.(238)
Stroke	0.59 (0.059)			3 months		[0.48; 0.71]		
Unstable angina	0.131 (0.013)			1 month		[0.11; 0.16]		
Transient ischemic attack	0.131 (0.013)			1 month		[0.11; 0.16]		

AE = adverse event; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; EQ-5D-5L = EuroQoL 5-Dimensions 5-Level; HSE = Health Survey for England; NICE = National Institute for Health and Care Excellence; SE = standard error

B.3.5. Cost and healthcare resource use identification, measurement and valuation

B.3.5.1. Resource identification, measurement and valuation studies

An SLR was conducted, with a cut-off date of 19 August 2024, to identify studies on the cost and healthcare resource use (HCRU) associated with uncontrolled COPD (Appendix I). Database searches (of MEDLINE, Embase, CDSR, CENTRAL and EconLit) yielded a total of 1,587 references, of which 418 were retrieved for full-text screening. Seven further references were identified via the companion Utilities SLR (Appendix H) and conference website searches. Following full-text screening, 93 references were included in the SLR. Of these, 37 citations (corresponding to 36 unique studies) were identified as either reporting data by GOLD severity, reporting outcomes associated with exacerbations, or reporting on hospitalised patients in Canada and Europe, and were prioritised for data extraction. Among the 36 unique studies, most were from Canada (12 studies), Spain (7 studies) or the US (6 studies); the remainder were from Sweden (2 studies), the UK (3 studies) and Denmark, Finland, France, Germany, Italy and Norway (1 study each).

The SLR did not identify any studies from the UK that categorised HCRU by severity, as required for our cost-effectiveness model. Health state unit costs are therefore derived from the 2018 NICE COPD economic model report NG115 and supplemented with cost data from NHS HES 2021/2022 (Section B.3.5.3).(189)

B.3.5.2. Intervention and comparator costs and resource use

Treatment acquisition costs are calculated based on the package price costs and the drug quantity required according to expected treatment schedules (detailed in Appendix K). Treatment schedules are based on the SmPCs for each individual treatment. Background therapy is a basket comparator (weighted between ICS + LAMA + LABA and LAMA + LABA products), as described in Section B.3.2.4. The cost of background therapy is calculated based on the specified proportion of individual treatments within the basket, along with the dosing schedules and unit costs of each treatment. Unit costs, package information and costs per model cycle for each treatment option in the model are derived from the British National Formulary (BNF).(239) No comparator products carry confidential discounts and so list prices are used.

Background therapy comprises only inhalers, which are self-administered, thus patients incur no administration cost. Dupilumab has a subcutaneous mode of administration, so patients may incur no administration cost if dupilumab is self-administered. In the base case, it is assumed that 100% of patients who receive dupilumab self-administer, and thus do not incur routine administration costs. Note that dupilumab for the COPD indication will be offered with the homecare service provided for the other reimbursed indications.

However, it is assumed that dupilumab patients receive subcutaneous self-injection training once by a hospital nurse and self-administer thereafter. Training is assumed to take one hour of nurse time and cost £48 (Hospital based nurse, Band 5).(240)

A summary of intervention and comparator costs included in the cost-effectiveness analysis is presented in Table 62.

The dosing of dupilumab is 300 mg given every other week by subcutaneous injection. The annual cost for dupilumab at list price is £16,500 PPPY. According to the confidential simple patient access scheme (approved by NHS England and Improvement and the Patient Access Scheme Liaison Unit in 2021) there is a [redacted]% discount off the list price of dupilumab corresponding to £[redacted] per pack of two 300 mg syringes or pens. In the model, the unit cost per dose is multiplied by the treatment frequency to estimate the cycle-specific drug costs.

Table 62. Annual unit costs associated with the technology in the economic model

Items	Dupilumab 300 mg every two weeks	Dupilumab 300 mg every two weeks + background therapy	Background therapy
Acquisition cost per pack (dupilumab)	£1,264.89 £[redacted] (at net price)	NA	NA
Acquisition cost (per cycle)	NA	£17,041.83 (at list price) £[redacted] (at net price)	£541.80
In hospital self-administration training cost (one-time)	£48 (Hospital based nurse band 5)(240)		NA

NA = not applicable

B.3.5.3. Health state unit costs and resource use

Calculation of disease management and exacerbation costs for each COPD stage involved application of a micro-costing approach. This methodology itemises and quantifies healthcare resource utilisation at the most granular level and identifies and multiplies suitable unit costs for each resource type. These are then summed across resources to arrive at the estimate used in the model. Patient resource utilisation is assumed to vary by COPD stage as well as by exacerbation occurrence.

B.3.5.3.1. COPD management costs

COPD management resource use frequencies are derived from the NICE NG115 COPD economic model report (Table 63).(189) This report has been selected due to its detailed stratification of annual COPD management resource use inputs according to GOLD severity which aligns with the stratification in our model.(189) Additionally, the lack of empirical data on primary and community care identified in our literature search necessitated the use of a reliable source. The NICE NG115 COPD economic model report provided detailed estimates based on the consensus of NICE committee members, making it a robust and credible source for our analysis.

Table 63. Annual COPD management resource use inputs

Resources	Annual frequency by health state[a]			
	Mild COPD	Moderate COPD	Severe COPD	Very Severe COPD
GP visit	1	1	1.5	2
Respiratory team visit	0	0	2	4
Outpatient visit	0	0	1	2
Spirometry	1	1	2	3
Pulmonary rehabilitation	0.02	0.03	0.06	0.09
Oral corticosteroids	0.88	0.96	1.7	2.7
Home oxygen therapy (proportion of patients)	0	0	0.05	0.4
Influenza vaccine (proportion of patients)	0.73	0.73	0.73	0.73
CT scan	0	0	0.05	0.1
Total annual cost (£)	100.44	102.86	809.94	1,523.26

COPD = chronic obstructive pulmonary disease; CT = computed tomography; GP = general practitioner
[a] Frequency unless stated otherwise
Source: NICE 2018 NG115 COPD economic model report(189)

The unit costs for the annual COPD management resources are derived from the National Schedule of NHS Costs 2022/2023, Personal Social Services Research Unit (PSSRU) 2023, BNF and relevant literature. Given that the inflation indices for 2024 have not yet been published as of October 2024, the costs are all based or have been adjusted to 2023 values using the NHS inflation indices (NHSII).(240)

The unit costs source for home oxygen therapy (Hertel et al. 2012)(241) is consistent with the NICE NG115 COPD economic model report.(189) The home oxygen therapy unit cost was inflated to the current value using Hospital and Community Health Service (HCHS) pay and price inflation indices and NHSII.

Table 64 presents the corresponding unit costs and their sources. Values from earlier publications are adjusted to current values using the HCHS index.

Table 64. Unit costs for COPD management resource use

Resources	Unit cost (£)*	Source
GP visit	49.00	PSSRU 2022/23 10 minute consultation(240)
Respiratory team visit	218.00	PSSRU 2022/23 - Episode assumed to comprise six 40-minute visits from either a band 6 (75%) or band 7 (25%) hospital nurse(240)
Outpatient visit	196.00	NHS Reference Costs 2022/23 – weighted average of respiratory medicine service outpatient procedures(242)
Spirometry	36.18	NHS Reference Costs 2010/2011 – outpatient spirometry test and bronchodilator response test – adjusted to current value(243)
Pulmonary rehabilitation	236.35	NHS Reference Costs 2022/23 – weighted average of pulmonary rehabilitation service outpatient procedures(242)

Resources	Unit cost (£)*	Source
Home oxygen therapy (proportion of patients)	20.11	Hertel et al. 2012(241)
Influenza vaccine (proportion of patients)	13.50	BNF Adjuvanted quadrivalent influenza vaccine (surface antigen, inactivated) suspension for injection 0.5ml pre-filled syringe(239)
CT scan	114.61	NHS Reference Costs 202/23 – weighted average of directly accessed CT scans, excluding 18 years and under(242)

*Unit costs have been inflated to 2023 values
BNF = British National Formulary; CT = computed tomography; GP = general practitioner; NHS = National Health Service; PSSRU = Personal Social Services Research Unit

B.3.5.3.2. Exacerbation cost

Moderate exacerbation

The resource use and frequencies for moderate exacerbations are sourced from the NICE NG115 COPD economic model report, based on the consensus of NICE committee members. However, we believe that GP visit resource use may be an underestimate.(167) Therefore, we have aligned with the ERG's approach from NICE TA461 regarding excess primary care contacts due to moderate exacerbations. NICE TA461 calculated additional GP visits from Thomas et al. 2014, a UK primary care observational study, which reported 6.67 primary care COPD contacts per year for patients with frequent exacerbations. The rate of additional GP visits for a moderate exacerbation aligns with clinical expert insights(167) and the recommendation by NICE that all individuals who have had a COPD exacerbation have primary care appointments once they are clinically stable.(244) Additionally, patients with COPD who frequently exacerbate will require frequent GP visits as sputum samples may be needed for culture and sensitivity testing for antibiotic resistance. Patients with frequent moderate exacerbations often require rescue packs containing antibiotics, making them susceptible to antibiotic resistance.(82, 83) However, due to a lack of robust evidence, we have made a simplifying assumption to not include sputum sampling and alternative antibiotic prescribing due to antibiotic resistance in this economic evaluation. Table 65 presents the inputs for resource use and unit costs associated with a moderate exacerbation.

Table 65. Moderate exacerbations and associated unit costs

Resources	Frequency per exacerbation	Resource use source	Unit costs (£)*	Unit cost source
A&E visit without admission	0.3	NICE NG115 COPD economic model report	104.37	NHS Reference Costs 2022/23 – weighted average of non-admitted emergency medicine entries
Respiratory team visit	0.1	NICE NG115 COPD economic model report	218.00	PSSRU 2022/23 - Episode assumed to comprise six 40-minute visits from either a band 6 (75%) or band 7 (25%) hospital nurse
GP visit	1	Thomas et al. 2014	49.00	PSSRU 2022/23 10-minute consultation
OCS (number of prescriptions)	1	NICE NG115 COPD	0.77	Drug Tariff Sep 2024 (prednisolone 5mg - 28 tablets)

Resources	Frequency per exacerbation	Resource use source	Unit costs (£)*	Unit cost source
		economic model report		
Antibiotics (number of prescriptions)	2	NICE NG115 COPD economic model report	1.08	Drug Tariff Sep 2024 (Amoxicillin 500mg -15 capsules)
Total annual cost (£)			105.04	

*Unit costs have been inflated to 2023 values.
A&E = accident and emergency; COPD = chronic obstructive pulmonary disease GP = general practitioner; OCS = oral corticosteroids; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSSRU = Personal Social Services Research Unit

Severe exacerbations

For severe exacerbations, clinical experts consulted during our advisory board reviewed the available sources (in particular Fenwick et al. 2021,(192) which provides a limited micro-costing approach to severe exacerbations) and advised that these underestimated both cost and resource use so likely did not capture the full burden on the NHS.(167) Consequently, a utilisation analysis has been conducted using the HES database, which includes details of all secondary care patient episodes at NHS hospitals in England (Appendix M).(123) Severe exacerbations were identified using the ICD-10 classification, covering the period from April 2018 to February 2024. For the purposes of this analysis, a severe exacerbation is defined as requiring a hospital stay.

The costing analysis utilised the NHS Reference Costs National Cost Collection datasets. Weighted averages have been calculated, considering the frequency and cost of all relevant currency codes for each resource associated with a severe COPD exacerbation. Table 66 shows the inputs for resource use and unit costs associated with a severe exacerbation.

Table 66. Severe exacerbations and associated unit costs

Resources	Frequency per exacerbation (based on Sanofi HES utilisation analysis)(123)	Unit costs (£)	Unit cost source
Ambulance transport	70%	244.09	NHS Reference Costs 2022/23 – weighted average of ambulance events
A&E admission	88%	312.49	NHS Reference Costs 2022/23 – weighted average of admitted emergency medicine entries
Hospital stay (LOS)	1 day	3,239.40	NHS Reference Costs 2022/23 – weighted average of COPD non-elective long stay, excluding one day or less category
ICU (LOS)	1%	2,330.22	NHS Reference Costs 2022/23 – weighted average of all non-specific, general adult critical care bed days
Readmission within 30 days	14%	3,239.40	NHS Reference Costs 2022/23 – weighted average of COPD non-elective long stay, excluding one day or less category

Resources	Frequency per exacerbation (based on Sanofi HES utilisation analysis)(123)	Unit costs (£)	Unit cost source
Ventilation	7%	1,080.62	NHS Reference Costs 2022/23 –non-elective, non-invasive ventilation, 19 years and over
Oxygen therapy	2%	265.57	NHS Reference Costs 2022/23 – non-elective oxygen assessment and monitoring
CT scan	10%	114.61	NHS Reference Costs 2022/23 – weighted average of directly access CT scans, excluding 18 years and under
Echocardiogram	5%	91.60	NHS Reference Costs 2022/23 – directly accessed simple echocardiograms, 19 years and over
CPAP therapy	1%	1,080.62	NHS Reference Costs 2022/23 - non-elective, non-invasive ventilation, 19 years and over
Follow-up outpatient appointments within 30 days of exacerbation	18%	166.77	NHS Reference Costs 2022/23 – weighted average of non-admitted follow-up outpatient attendances
Follow-up outpatient appointments within 90 days of exacerbation	37%	166.77	NHS Reference Costs 2022/23 – weighted average of non-admitted follow-up outpatient attendances
Total annual cost (£)		4,361.60	

A&E = accident and emergency; CPAP = continuous positive airway pressure; CT = computed tomography; HES = hospital episode statistics; ICU = intensive care unit; LOS = length of stay
Source: Sanofi 2024 HES utilisation analysis for severe exacerbations;(123) NHS Reference Costs 2022/23 National Cost Collection(242)

B.3.5.3.3. Cardiovascular Events

Patients who experience acute exacerbations due to COPD also have an elevated risk of CV events, which is accounted for in the model. A fixed proportion of patients in each exacerbation health state accrue costs and disutilities specific to CV events. The incidence of non-fatal CV events in the trial period is derived directly from the pooled trials (Table 67), while the incidence of non-fatal CV events in the Markov period (stratified by exacerbation-related states) is derived from a post-hoc analysis of the large international SUMMIT RCT, in lieu of relevant UK data (Table 68).(86) Fatal CV events are not considered in the model due to very low incidence.

Table 67. Incidence of CV events during the trial period

Treatment	Pooled (BOREAS + NOTUS), %[a]
Dupilumab + background therapy	0.7
Background therapy	1.7

CV = cardiovascular
[a] The CV event incidence for the selected trial is the same for each subgroup within the selected trial due to small sample size.
Source: Sanofi 2023 [Data on file] Pooled analysis – Summary of Clinical Safety(177)

Table 68. Incidence of CV events in the Markov period

Exacerbation State	Incidence, %
No exacerbation[a]	1.3
Moderate exacerbation[b]	2.8
Severe exacerbation[b]	4.1

CV = cardiovascular; HR = hazard ratio
[a] Among patients without an acute exacerbation event, 487 patients experienced a CV event in 21,624 patient-years, thus leading to an HR of 0.022. The HR was converted to an annual transition probability.
[b] The probability of patients who experience CV events post moderate/severe exacerbation is calculated based on the sum of hazards of CV events in the 1 to 30 days post-exacerbation, 31 to 90 days post-exacerbation, and 90+ days post-exacerbation, based on the respective HRs.
Source: Kunisaki et al. 2018(86)

The composite CV event is further split into myocardial infarction, stroke, unstable angina and transient ischemic attack. Note that only non-fatal CV events are considered in the model due to the simplistic assumption that CV events are modelled as an AE and not as a specific health state. The breakdown of a composite CV event into individual non-fatal CV events is derived from Kunisaki et al.(86) It is assumed that the breakdown of CV events is the same in both the trial period and the Markov period. The CV event management cost in the model is calculated as a weighted product of the composite CV event probability, the individual breakdown of CV events and the corresponding unit costs (Table 69).

Table 69. Breakdown of composite CV events and associated costs

CV event	Breakdown, %	Unit cost (acute)	Unit cost (follow-up)
Myocardial infarction	41.5	£2,074.28	£0
Unstable angina	30.5	£3,531.61	
Stroke	19.9	£1,055.79	
Transient ischemic attack	8.2	£1,333.18	
Source	Kunisaki et al. (adjusted for non-fatal CV events only)(86)	NHS reference costs(245)	Conservative assumption[a]

CV = cardiovascular; NHS = National Health Service
[a] Both the acute and follow-up costs are applied in the same year. Follow-up costs refer to disease management costs incurred by the patients in the year of CV events.

B.3.5.4. Adverse event unit costs and resource use

The model calculates an aggregated cost of AE management for each treatment (Table 70). Since the AEs included in the model are not severe, the unit costs are assumed to be the cost incurred for one GP visit. Costs are sourced from 2022/23 PSSRU based on a 10 minute consultation.(240)

Table 70. List of adverse events and summary of costs in the economic model

AE	Frequency, %		Unit cost
	Dupilumab + background therapy	Background therapy	
Headache	7.8	6.6	£49
Back pain	4.5	3.1	£49
Urinary tract infection	3.0	1.9	£49

AE	Frequency, %		Unit cost
	Dupilumab + background therapy	Background therapy	
Gastritis	2.0	0.7	£49
Hypertension	3.4	4.6	£49
AE management cost per cycle	£17.39	£14.2	NA

AE = adverse event; NA = not applicable
Source: Sanofi 2023 [Data on file] Pooled analysis summary of clinical safety(177); PSSRU 2022/23(240)

B.3.5.5. Miscellaneous unit costs and resource use

Indirect costs are included in a sensitivity analysis and include productivity loss and early retirement. No statistics on caregiving costs for patients with COPD in England were identified, therefore they have not been considered.

B.3.5.5.1. Travel costs

Travel costs have not been included for the following reasons:

- For severe exacerbations, we have assumed patients use ambulatory services and this is already captured as part of exacerbations costs (Section B.3.5.3.2).
- For moderate exacerbations, we have assumed zero transport costs as they are managed in the GP setting or at home.

B.3.5.5.1. Productivity loss

Patients with COPD take days off work and thus incur a productivity loss. Similarly, the majority of patients with COPD require informal carer support resulting in financial impact.(119) (35) The model considers the number of days per month a patient misses work. This is applied for patients of working age only; at each cycle, the proportion of patients below the age of retirement is calculated based on the normal distribution centred at the mean age of retirement. To avoid double counting, the model considers the missed workdays stratified by COPD stage as well as exacerbation status, as shown in Table 71. Days missed per month, excluding exacerbation events, were derived by dividing the values reported by Jansson et al 2013(246) by 12.

To calculate the days lost due to moderate exacerbations half a day of work was assumed to be missed due to a moderate exacerbation to account for a visit to the GP and pick up a rescue pack from the pharmacy. This was multiplied by the number of moderate COPD exacerbations (1.9) experienced within 1 year before the first visit from the pooled NOTUS and BOREAS trials.(174)

For severe exacerbations, data for non-elective COPD hospitalisations using the HES database were analysed to derive the average duration of hospital stay (5.25).(57) Similarly to the moderate exacerbation, this time period was multiplied by the number of severe COPD exacerbations (0.3) experienced within 1 year before the first visit from the pooled NOTUS and BOREAS trials.(174)

Based on the average annual salary specified in Table 71, productivity loss per cycle is calculated by calculating the annual wage lost due to COPD.

Table 71. Summary of productivity losses

COPD stage	Productivity loss (days per month)	Productivity loss (days per cycle)	Source
Mild COPD	0.095	1.14	Jansson et al. 2013(246)
Moderate COPD	0.059	0.71	Jansson et al. 2013(246)
Severe COPD	1.00	12	Jansson et al. 2013(246)
Very severe COPD	1.883	22.6	Jansson et al. 2013(246)
Moderate exacerbation	0.079	0.95	Calculation based on assumed half day multiplied by rate of moderate exacerbations from pooled trial data.
Severe exacerbation	0.131	1.575	Calculation based on HES data for non-elective hospitalisation(57), dividing total bed days by the sum of admissions. Then total days multiplied by rate of severe exacerbations from pooled trial data.

COPD = chronic obstructive pulmonary disease

The productivity loss is only applicable for patients who are below the age of retirement and employed (early retirees are excluded from the calculation; Table 73). The age of retirement was assumed to be 66 and the % of patients employed is 78.2%. The proportion of patients below the age of retirement was calculated assuming a normal distribution centred around the retirement age. Based on the number of productivity loss per cycle, the productivity costs are calculated by COPD stage, and the additional productivity loss is calculated per exacerbation.

Table 72. Summary of employment inputs

Parameter	Mean	SD	Note
Retirement Age	65	8.2	A normal distribution centred at 66 is used to determine the proportion of patients who are below the age of retirement; https://www.fool.co.uk/personal-finance/research/average-retirement-age-in-the-uk/(247)
% employed under the retirement age	75.7%	0.0757	https://www.statista.com/statistics/280228/uk-employment-rate-by-age-group/(248)
Average annual salary	£35,830	£3,583	https://www.forbes.com/uk/advisor/business/average-uk-salary-by-age/(249)
Number of working days in a year	256	NA	Assumption

NA = not applicable; SD = standard deviation

B.3.5.5.2. Early retirement loss

Early retirement is considered based on the proportion of patients who retire early stratified by COPD stage. At each cycle, the proportion of patients below the age of retirement is calculated based on the normal distribution centred at the mean age of retirement. The retirement inputs are summarised in Table 72. The proportion of patients who retire early is specified by COPD stage, as summarised in

Table 73. As data for the UK were not available by COPD stage, results of an analysis of German electronic health records (COSYCNET; N=2,139) were used which showed that the 34.7%, 36.6%, 51.4% and 72.2% of patients with COPD Grade1, 2, 3 and 4, respectively, retired early.(129) This was higher than early retirement in the control group where only 14.7% of people retired early.(129) To estimate the excess retirement rate attributable to COPD, the control group rate was subtracted from each COPD stage-specific rate.

Table 73. Early retirement proportion stratified by COPD stage

COPD stage	Early retirement, %	Source
Mild COPD	20.0	Wacker et al. 2016(129)
Moderate COPD	21.9	
Severe COPD	36.7	
Very severe COPD	57.5	

COPD = chronic obstructive pulmonary disease

Based on the proportion of patients who retire early by COPD stage, the proportion of patients below the age of retirement (normal distribution centred around the retirement age), the number of working days in a year (adjusted for the days that patients lose out on productivity loss) and the average annual salary, the early retirement cost stratified by COPD stage is calculated per cycle.

Table 74 shows the indirect costs per cycle due to loss of work and early retirement if it were to be included in the model.

Table 74. Indirect costs per cycle due to loss of work and early retirement by COPD stage

COPD Stage	Total indirect costs due to loss of work per cycle	Total indirect costs due to early retirement per cycle
Mild COPD	£160	£7,134
Moderate COPD	£99	£7,825
Severe COPD	£1,680	£12,533
Very severe COPD	£3,163	£18,783

COPD = chronic obstructive pulmonary disease
[a]In order to avoid double counting, the days patients lose out due to productivity losses are not included in the adjusted working days

B.3.6. Severity

We do not expect the severity modifier to apply to this appraisal.

B.3.7. Uncertainty

There are several challenges with modelling the course of COPD and long-term treatment effect of dupilumab. One such challenge is capturing the dynamic relationship between exacerbations and disease progression. The frequency and severity of exacerbations is dependent on GOLD stage in the model, as with previous models identified (Section B.3.1), but not vice versa. In reality,

exacerbations impact the trajectory of FEV_1 decline;(192, 195) however, this interdependency is not fully captured because of limitations of a conventional Markov structure.

There is also uncertainty around the extrapolation of trial data beyond the follow-up period. Dupilumab is the first biologic used to treat moderate-to-severe COPD and so, as is typical for newly approved agents targeting chronic conditions, long-term treatment effect data are limited. Sensitivity and scenario analyses evaluate the uncertainty surrounding the consequent use of external data and assumptions in long-term predictions (Section B.3.11).

B.3.8. Managed access proposal

No managed access proposal is included in this submission.

B.3.9. Summary of base case analysis inputs and assumptions

B.3.9.1. Summary of base case analysis inputs

A summary of the inputs used in the base case analysis is provided in Table 75.

Table 75. Summary of base case inputs

Variable	Value	Measurement of uncertainty (distribution)	Reference/corresponding section in this report
Model characteristics			
Perspective	Healthcare payer (NHS and personal social services (PSS)	N/A	NICE reference case; Section B.3.2.2
Patient population	Full licenced patient population for the pooled BOREAS and NOTUS populations	N/A	MHRA label; Section B.3.2.2
Time horizon	Lifetime (until the cohort reaches 100 years of age)	N/A	Assumption
Discount rate: costs and outcomes	3.5%	N/A	NICE manual(198)
Clinical parameters			
Response assessment at 52 weeks	The efficacy response criterion for continued treatment at 52 weeks considered a patient to be a non-responder if they experience more severe exacerbations on treatment than the year prior to treatment AND/OR, in the case of equal numbers of severe exacerbations, if they experience more moderate exacerbations than the year prior to treatment.	N/A	Section B.3.3.2

Variable	Value	Measurement of uncertainty (distribution)	Reference/corresponding section in this report
Annual discontinuation rate first 52 weeks	9.3%	N/A	Pooled analysis of BOREAS and NOTUS;(174) Section B.3.3.7
Annual discontinuation rate beyond 52 weeks	15.0%	N/A	Advisory board conducted by Sanofi in July 2024 with five respiratory clinicians and two health economists;(138) Section B.3.3.7
FEV_1 treatment effect duration	Dupilumab: 2 years Placebo: 0 years	N/A	TRAVERSE;(209) Section B.3.3.6.1
Baseline exacerbation rate	Based on patient data from the year prior to randomisation	N/A	Section B.3.3.3.1B.3.3.3.1
Transition probabilities within COPD stage	Based on UK RWE	N/A	Whittaker et al. 2022;(26) Section B.3.3.5
Transition probabilities across COPD stage	Based on RWE on FEV_1 decline from the TORCH study, with a Type 2 inflammation modifier based on the CanCOLD study	N/A	Fenwick et al. 2021(192) and Tan et al. 2021(41); Section B.3.3.6
Mortality due to COPD stages	Based on UK RWE	N/A	Whittaker et al. 2024;(30) Section B.3.3.8.2
Excess mortality due to exacerbation	15.6% (case-fatality rate for severe exacerbation)	95% CI: 10.9, 20.3	Hoogendoorn et al. 2011;(222) Section B.3.3.8.3
Health effects			
Health state utilities	Mapping exercise conducted by Sanofi	N/A	Section B.3.4.2
Disutilities associated with exacerbations	Acute and chronic utility decrement applied for moderate and severe exacerbations	N/A	Section B.3.4.5
Disutilities associated with CV events	Different disutilities applied depending on type of event	N/A	Sterne et al. 2017;(238) Section B.3.4.6
Disutilities associated with AEs	Assumed to be 0	N/A	Assumption; Section B.3.4.6
Cost and healthcare resource use			
Disease management costs	Various depending on GOLD severity	N/A	Unit costs from the National Schedule of NHS Costs 2022/2023, PSSRU 2023, BNF and relevant literature, adjusted to 2023 values; Section B.3.5.3.1
Moderate exacerbation costs	£105.04	N/A	Resource used based on NICE NG115 COPD economic model report(189) and NICE TA461; Section B.3.5.3.2
Severe exacerbation costs	£4,361.6	N/A	Utilisation analysis using the HES database;(123) costing analysis using the 2022/23 National Cost Collection; Section B.3.5.3.2
Drug acquisition	Various depending on treatment	N/A	BNF list prices plus treatment schedules based on SmPCs; Section B.3.5.2

Variable	Value	Measurement of uncertainty (distribution)	Reference/corresponding section in this report
CV events	Various depending on type of event	N/A	NHS reference costs(245); Section B.3.5.3.3
AE costs	£49 (cost of one GP visit)	N/A	2022/23 PSSRU;(240) Section B.3.5.4

AE = adverse event; BNF = British National Formulary; CanCOLD = Canadian Cohort of Obstructive Lung Disease; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; FEV_1 = forced expiratory volume in one second; GP = general practitioner; HES = Hospital Episode Statistics; MHRA = Medicines and Healthcare products Regulatory Agency; N/A = not applicable; NHS = National Health Service; PSS = Personal Social Services; PSSRU = Personal Social Services Research Unit; RWE = real-world evidence; TORCH = Towards a Revolution in COPD Health; UK = United Kingdom

B.3.9.2. Assumptions

A summary of the key assumptions made in the economic model, alongside their justifications, is provided in Table 76.

Table 76. Summary of model assumptions

Assumptions	Justifications	Addressed in scenario analyses
The BOREAS and NOTUS clinical trials are equivalent	The clinical trials were designed to confirm and replicate each other's findings. The main difference in the studies was the upper age limit for NOTUS was 85 years but the BOREAS age limit was 80 years.	No. The pooled ITT data from the clinical trials is used in the analysis to make best use of all the available data.
The plateau in lung function observed in the trials from Week 2 through to Week 52 is maintained for both treatment arms	The trial data show improvement in lung function was observed within 2 weeks after the initiation of dupilumab or background therapy and was sustained through Week 52.	No. Transitions across COPD stage in the decision tree are not allowed.
CV events are modelled as a composite AE and not as a specific health state. The breakdown of composite CV events is assumed to be the same in the trial and post-trial periods	Simplifying assumption. The composite CV event is split into myocardial infarction, stroke, unstable angina and transient ischemic attack derived from Kunisaki et al. 2018.(86)	No.
Patients who experience moderate exacerbations do not experience any excess mortality	Simplifying assumption. A fixed probability of 15.6% of death derived from Hoogendorn et al. 2011 is applied to patients who experience a severe exacerbation.(222)	Yes. An alternative source (Whittaker et al. 2022) for mortality which includes exacerbation severity is provided.(26)
Responders will continue to receive dupilumab in the real world after 52 weeks while non-responders switch to receiving background therapy only	Common modelling practice. A response assessment at the end of Week 52 of treatment with dupilumab is applied as might be expected in clinical practice. Following this, an annual discontinuation rate models all-cause withdrawal.	No
Patients who discontinue in the decision tree do so at Week 52	Patients who discontinue in the first year still accrue costs for dupilumab until the end of	No. The decision tree does not allow for intermediate assessments beyond Week 2.

Assumptions	Justifications	Addressed in scenario analyses
	Week 52. This may not be the case in the real world.	
Annual discontinuation beyond the trials is assumed to be 15%	Asthma in dupilumab homecare data(216) and advisory board conducted by Sanofi in July 2024 with five respiratory clinicians and two health economists.(167)	Yes. • Higher estimates from clinical expert elicitation (20% and 25.8%).(167) • Asthma biologics discontinuation rate observed in the real world (22.4%).(220)
Patients on background therapy remain on treatment at all times	Highly conservative assumption as it is known adherence to inhalers is low.	No. There is no evidence to support any difference in long-term inhaler use between prior dupilumab treated and non-dupilumab treated patients.
The distribution of patients with 1, 2, and 3+ exacerbations observed in the selected trials is constant throughout the horizon	Simplifying assumption.	No long-term data to inform this distribution beyond the observed trial period of 1 year.
Patients with Type 2 inflammation experience a faster decline in FEV_1 over time compared to COPD patients without Type 2 inflammation	The CanCOLD study (N=1,120) found that COPD patients with high blood EOS levels were associated with more rapid FEV_1 decline.(41)	Yes, a scenario where an unadjusted Fenwick risk equation is included, while the base case uses a modified Fenwick risk equation to model the natural history decline of FEV_1, representing the accelerated decline in patients with Type 2 inflammation.
Patients on dupilumab + background therapy experience an FEV_1 treatment effect period of 2 years beyond the trial, whereas the treatment effect for background therapy alone is assumed to wane immediately after the end of the 52-week period.	Efficacy results from a dupilumab asthma trial indicate that TRAVERSE, used as a proxy measure due to the lack of long-term COPD data, demonstrates that lung function benefits were sustained for two years after the conclusion of the one-year RCTs.(209)	Yes, an alternative scenario where patients on dupilumab + background therapy experience an FEV_1 treatment effect period of 1 years beyond the trial, has been included based on the views of clinical experts gathered through a structured expert elicitation (see Appendix P).
The baseline exacerbation rate for both dupilumab and background therapy sourced from the year prior to randomisation data from the pooled ITT trial data.	To mitigate the expected low exacerbation rates observed in clinical trials compared with the real world while keeping as closely as possible to the trial population data, we have used patient data (placebo and dupilumab combined) from the year prior to randomisation as the baseline exacerbation rate	Yes, two alternative scenarios have been considered, each with different baseline exacerbation sources: pooled ITT trial-based exacerbation rates from the trial and RWE exacerbation rates from the CPRD-HES database. (59)
Post trial exacerbation transitions are based on the adjusted incidence rate ratios from Whittaker et al. 2022. (26)	No granular data are available from the dupilumab trials or RWE to inform the subsequent exacerbation risk associated with the frequency of prior exacerbations.	Yes, a scenario where both the baseline exacerbations and the post-trial exacerbation transitions are from the pooled ITT trial data.
Utility and disutility values mapped from SGRQ to EQ-5D accurately reflect consistently collected EQ-5D data from both BOREAS and NOTUS clinical trials.	The mapped SGRQ utility values used in the model align more closely with the inconsistently collected EQ-5D values from NOTUS than with alternative algorithms found in the literature (see Appendix Q).	Yes, a scenario has been included where the inconsistently collected EQ-5D data directly captured in the NOTUS study is used.

AE = adverse event; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; EOS = eosinophils; FEV_1 = forced expiratory volume in 1 second; ITT = intent-to-treat

B.3.10. Base case results

The expected positioning of dupilumab in UK clinical practice is for adults with uncontrolled COPD (≥2 moderate or ≥1 severe historical exacerbations within 12 months) and raised EOS (≥300 cells/μL; Type 2 inflammation), on triple inhaled therapy (LABA + LAMA + ICS) or double therapy (LABA + LAMA) where ICS is not appropriate. This reflects the full licensed indication for dupilumab in COPD as described in the scope and decision problem. In line with this full licence positioning, we present results for the full analysis sets for the pooled BOREAS and NOTUS populations below. The base case results are calculated based on the key parameters listed in Table 75. Results from the deterministic analysis for the base case are presented in Table 77. Disaggregated results of the model are provided in Appendix J.

Table 77. Base case deterministic results

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,668
Background Therapy	[redacted]	[redacted]	[redacted]				

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

At the patient access scheme price, dupilumab plus background therapy and background therapy alone accumulated costs of £[redacted] and £[redacted], and total quality-adjusted life-years (QALYs) of [redacted] and [redacted], respectively. The ICER was £25,668/QALY which is within the range commonly considered cost-effective for the NHS, as it falls below the conventional NICE willingness-to-pay threshold (WTP) of £30,000 per QALY.

These results demonstrate that dupilumab is an appropriate use of NHS resources. Particularly notable is the scale of QALY gain given this is a treatment used as an add-on to maximal inhaled therapy and the poor starting health state of the patients eligible for treatment.

B.3.11. Exploring uncertainty

B.3.11.1. Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) has been conducted to assess the parametric uncertainty associated with the base case model results. All key parameters were assigned probability distributions from which random sampling was done over 1000 simulations (based on the convergence test). Where uncertainty data were not available for an input, standard errors of 20% of the mean values were assumed. For the RR for severe exacerbations vs background 50% was used and for the mild and very severe RR for moderate exacerbations 50% was also used on the basis of low patient numbers in these categories in the studies. The PSA results are presented in Table 78. The results align with the deterministic results.

Table 78. Summary of PSA results

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,793
Background Therapy	[redacted]	[redacted]	[redacted]				

CI = confidence interval; ICER = incremental cost-effectiveness ratio; LY = life year; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

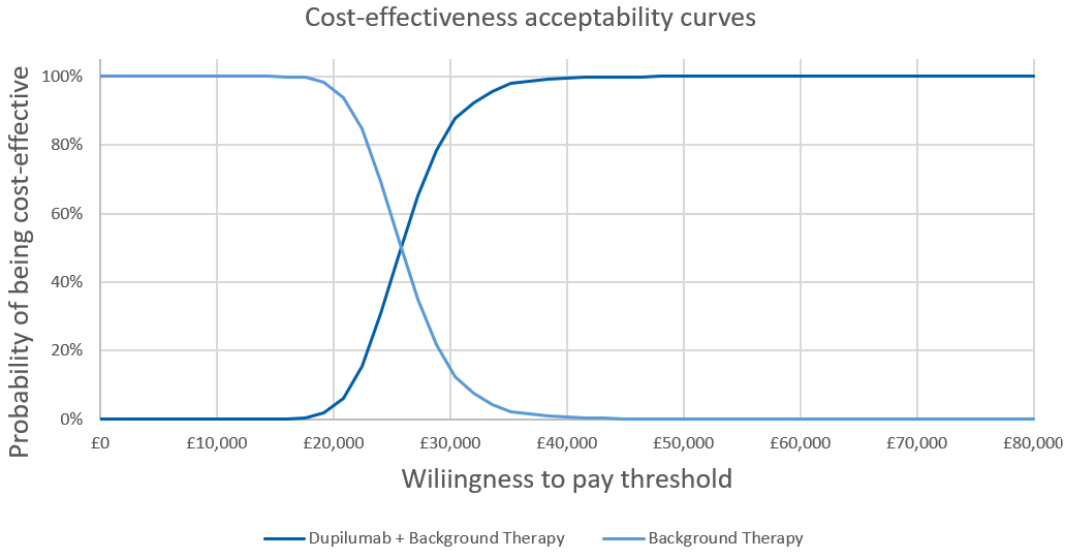
In addition, the incremental PSA results and cost-effectiveness acceptability curve (CEAC) are presented in Figure 31 and Figure 32, respectively. At a WTP of £30,000/QALY, the probability of being cost-effective is 81%; at £20,000 it is 3%.

Figure 31. Scatter plot for incremental cost-effectiveness results (1,000 iterations)

[redacted]

PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

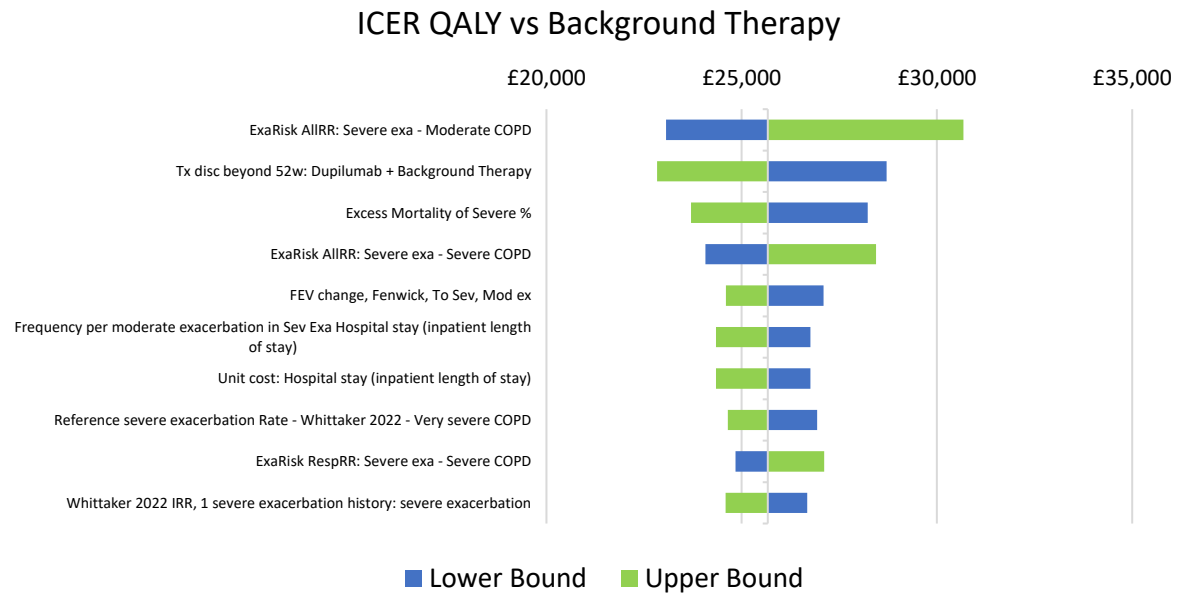
Figure 32. Cost-effectiveness acceptability curve (1,000 iterations



B.3.11.2. Deterministic sensitivity analysis

Model inputs used for the base case analysis are varied in a one-way deterministic sensitivity analysis (DSA), changing their values one by one within the ranges provided for dupilumab + background therapy vs. background therapy only (Figure 33). As shown in the tornado chart and Table 79, the top three drivers of the results are the parameters associated with the risk for severe exacerbations, treatment discontinuation and excess mortality for severe exacerbations.

Figure 33. Tornado diagram of ICER (incremental cost per QALY gained) of dupilumab + background therapy vs. background therapy



COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; ICER = incremental cost-effectiveness ratio; IRR = incidence rate ratio; QALY = quality-adjusted life year; Tx = treatment; w = weeks

Table 79. Top 10 drivers of the ICER results

Rank	Parameter	ICER - Lower Bound	ICER - Upper Bound	Difference
Base case ICER		**£25,668**		
1	ExaRisk AllRR: Severe exa - Moderate COPD	£23,066	£30,682	£7,615
2	Tx disc beyond 52w: Dupilumab + Background Therapy	£28,712	£22,832	£5,880
3	Excess Mortality of Severe %	£28,229	£23,705	£4,525
4	ExaRisk AllRR: Severe exa - Severe COPD	£24,070	£28,442	£4,371
5	FEV change, Fenwick, To Sev, Mod ex	£27,096	£24,593	£2,502
6	Frequency per moderate exacerbation in Sev Exa Hospital stay (inpatient length of stay)	£26,761	£24,342	£2,419
7	Unit cost: Hospital stay (inpatient length of stay)	£26,761	£24,342	£2,419
8	Reference severe exacerbation Rate - Whittaker 2022 - Very severe COPD	£26,929	£24,641	£2,288
9	ExaRisk RespRR: Severe exa - Severe COPD	£24,844	£27,112	£2,268
10	Whittaker 2022 IRR, 1 severe exacerbation history: severe exacerbation	£26,675	£24,586	£2,089

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; ICER = incremental cost-effectiveness ratio; IRR = incidence rate ratio; QALY = quality-adjusted life year

B.3.11.3. Scenario analysis

In order to test the uncertainty of the cost-effectiveness results due to the key parameters and assumptions, various scenario analyses have been explored (Table 80). A detailed description of the scenarios is included in Appendix N.

Table 80. Scenario analysis results – PAS price

Parameter	Scenario	Incr. QALYs	Incr. costs	ICER*	Rationale
Base case	**N/A**	[redacted]	[redacted]	£25,668	**N/A**
		[redacted]	[redacted]	£25,793	
Discount, cost	3%	[redacted]	[redacted]	£26,326	Alternative input to the NICE reference case.
		[redacted]	[redacted]	£26,476	
	5%	[redacted]	[redacted]	£23,891	
		[redacted]	[redacted]	£23,943	
Discount, health	3%	[redacted]	[redacted]	£24,431	
		[redacted]	[redacted]	£24 507	
	5%	[redacted]	[redacted]	£29,620	
		[redacted]	[redacted]	£29,784	
Time horizon	5 years	[redacted]	[redacted]	£68,201	
		[redacted]	[redacted]	£69,980	
	10 years	[redacted]	[redacted]	£35,693	
		[redacted]	[redacted]	£35,832	
	20 years	[redacted]	[redacted]	£26,121	
		[redacted]	[redacted]	£26,286	
Annual discontinuation rate beyond 52 weeks	22.4%	[redacted]	[redacted]	£22,416	This percentage is derived from the average discontinuation rate of biologic therapy from UK Severe Asthma Registry identified by Mansur et al. 2022.(220)
		[redacted]	[redacted]	£22,605	
	25.84%	[redacted]	[redacted]	£21,184	This scenario represents the views of clinical experts gathered through a structured expert elicitation.
		[redacted]	[redacted]	£21,586	

Parameter	Scenario	Incr. QALYs	Incr. costs	ICER*	Rationale
FEV_1 treatment effect duration	Dupilumab + background therapy - 1 years; background therapy - 0 year	[redacted]	[redacted]	£29,737	This scenario represents the views of clinical experts gathered through a structured expert elicitation.
		[redacted]	[redacted]	£30,251	
Baseline exacerbation rate	Background therapy - RWE; Dupilumab + background therapy - RR vs background therapy alone	[redacted]	[redacted]	£26,025	To reflect real-world exacerbation rates from Type 2 uncontrolled COPD patients in the UK.
		[redacted]	[redacted]	£26,181	
	Background therapy – Pooled BOREAS and NOTUS (taken during the trial); Dupilumab + background therapy - RR vs background therapy alone	[redacted]	[redacted]	£29,456	Exploratory scenario utilising in-trial exacerbation rates.
		[redacted]	[redacted]	£30,098	
Markov transition probabilities (transitions related to exacerbation)	Background therapy - Pooled BOREAS and NOTUS; Dupilumab + background therapy - RR vs background therapy alone With pooled ITT baseline exacerbation taken during the trial	[redacted]	[redacted]	£52,376	Exploratory scenario using trial data. This scenario is considered extreme because studies have shown that cumulative prior exacerbations can predict future exacerbations.
		[redacted]	[redacted]	£55,024	
Utilities	Mean adjusted CFB (LS-Regression-CW-NOTUS) for COPD as well as exacerbation disutilities	[redacted]	[redacted]	£26,100	Utility values based on trial data from NOTUS EQ-5D-5L, using the UK crosswalk tariff (Hernandez 2020), taken
		[redacted]	[redacted]	£26,209	

Parameter	Scenario	Incr. QALYs	Incr. costs	ICER*	Rationale
					from Week 24 and 52 only.
	Spencer et al. 2005 & Sadatsafavi et al. 2019 with exacerbation disutilities from Rutten Van Molken et al. 2009	[redacted]	[redacted]	£23,875	Alternative source from published literature.
		[redacted]	[redacted]	£24,118	
	Rutten Van Molken et al. 2006 with exacerbation disutilities from Rutten Van Molken et al. 2009	[redacted]	[redacted]	£22,577	The utility value is derived from published literature and aligns with the utility source from NICE NG115 COPD economic model report.
		[redacted]	[redacted]	£23,108	
	Borg et al. 2004 with exacerbation disutilities from Rutten Van Molken et al. 2009	[redacted]	[redacted]	£21,762	Alternative source from published literature.
		[redacted]	[redacted]	£21,770	
Excess mortality due to GOLD severity	Shavelle et al. 2009	[redacted]	[redacted]	£26,186	Shavelle et al. 2009 was used as an alternative mortality source from published literature, with mortality stratified based on non-exacerbation-related mortality as per Trigueros et al.
		[redacted]	[redacted]	£26,363	
	Leivseth et al. 2013	[redacted]	[redacted]	£26,005	An alternative mortality source from a Norwegian RWE study involving 1,540 patients, which was utilised in the NICE NG145 guideline model report.
		[redacted]	[redacted]	£25,975	

Parameter	Scenario	Incr. QALYs	Incr. costs	ICER*	Rationale
Excess mortality due to exacerbation	Whittaker et al. 2022	[redacted]	[redacted]	£38,733	An alternative source that provides mortality rates for both moderate and severe exacerbations.
		[redacted]	[redacted]	£38,840	
FEV_1 treatment effect beyond the trial	Unadjusted FEV_1 trajectory according to Fenwick	[redacted]	[redacted]	£28,308	To reflect the transitions from the original Fenwick equation without modifications, representing the accelerated FEV_1 decline in patients with Type 2 inflammation.
		[redacted]	[redacted]	£28,870	
Societal impact	Include societal perspective comprising loss of productivity and early retirement for patients only	[redacted]	[redacted]	£25,492	To reflect the potential impact on wider society
		[redacted]	[redacted]	£26,107	

*The deterministic ICER is first followed by the probabilistic ICER in each category. CFB = change from baseline; COPD = chronic obstructive pulmonary disease; CW = crosswalk; EQ-5D-5L = EuroQoL 5-Dimensions 5-Level; FEV_1 = forced expiratory volume in 1 second; ICER = incremental cost-effectiveness ratio; ITT = intent-to-treat; LS = least squares; N/A= not applicable; NICE = National Institute for Health and Care Excellence; PAS = patient access scheme; RR = risk ratio; RWE = real world evidence; UK = United Kingdom

B.3.11.4. Exploratory analysis comparing dupilumab with roflumilast

We have discussed the inappropriateness of the comparison with roflumilast and the technical difficulties associated with making a robust ITC in Sections B.2.9 and B.3.2.4.2 as well as Appendix D and T. However, to meet the requirements of the scope we have provided a comparison below. These data should be treated with caution.

The alternative model settings applied to the comparison vs roflumilast are provided in Table 81. All other settings are according to the dupilumab base case vs triple therapy.

Table 81. Summary of the parameter settings used for the comparison vs roflumilast

Variable	Value	Place in model	Justification
Annual probability of discontinuation: First 52 weeks	28%	[General inputs!L28]	In the RE2SPOND and REACT studies, 28.6% and 27.8% of patients treated with roflumilast discontinued treatment. In real-world practice, AEs, particularly

Variable	Value	Place in model	Justification
			gastrointestinal effects, lead to much higher discontinuation rates of around 70%.(136, 137, 144, 146) This is tested in sensitivity analysis.
Annual probability of discontinuation: beyond 52 weeks	100%	[General inputs!M28]	Clinical opinion suggests that all patients will have discontinued by the end of 2 years following initiation.
FEV_1 treatment effect duration	2 year	[General inputs!L57]	Conservative assumption that FEV_1 trial benefit will be retained for as long as dupilumab before onset of decline.
Efficacy response criterion: responders remaining on treatment at the end of year 1	100%	[General inputs!K228]	In TA461 there is no 'efficacy response criterion' for roflumilast so the proportion of patients moving into the Markov model who have not discontinued during year 1 is set to 100%.
GOLD severity breakdown at trial start. Severe COPD	100%	User defined: [General inputs!K79]	Roflumilast is recommended for patients with severe or very severe COPD. Overlap with the dupilumab trial population is in severe population only.
Source for roflumilast exacerbation probability	RR vs background therapy alone	[Markov transitions!M63]	Use of the direct roflumilast data. Tested in sensitivity analysis using exacerbation rates equivalent to dupilumab (Section B.2.9).
Source for RR for roflumilast exacerbations	RR vs background therapy alone	Table: [General inputs!J136:R141]	Use of the direct roflumilast data. Tested in sensitivity analysis using exacerbation rates equivalent to dupilumab (Section B.2.9).
AEs	1	Tables [CV events!] and [AE costs!]	Section B.2.9. Very conservative assumption as AEs in the real world are known to be a significant influence on discontinuations. Tested in Sensitivity analysis
Cost of roflumilast	£37.71 per pack of 30 500mg tablets	[Drug Acq and Admin!J71]	List price (no PAS is applicable to roflumilast).
Health state utility	Spencer & Sadatsafavi	[Utilities!G17] and [Utilities!F21]	Treatment-specific utility information is not available for roflumilast so health state utilities according to the most recent literature values are applied.

AE = adverse event; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; FEV_1 = forced expiratory volume in one second; ITC = indirect treatment comparison; PAS = patient access scheme; RR = rate ratio

The deterministic cost-effectiveness results are provided for the comparison with roflumilast in

Table 82.

Table 82. Incremental cost-effectiveness results for the exploratory analysis vs. roflumilast

Treatments	TOTAL Lys	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Probabilistic results (1,000 runs)							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£62,959
Roflumilast + Background Therapy	[redacted]	[redacted]	[redacted]				
Deterministic results							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£60,121
Roflumilast + Background Therapy	[redacted]	[redacted]	[redacted]				

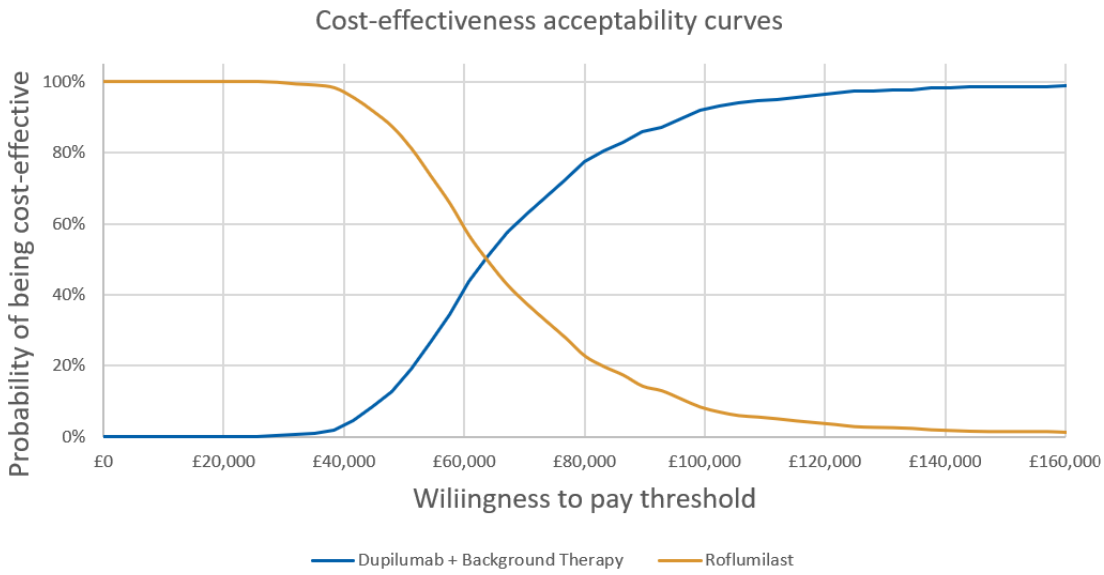
ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

In addition, the incremental PSA results and CEAC curve are presented in Figure 34 and Figure 35, respectively. At a WTP of £30,000/QALY, the probability of being cost-effective is 0%; at £20,000 it is 0%.

Figure 34. Scatter plot for incremental cost-effectiveness results (1,000 iterations)

PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 35. Cost-effectiveness acceptability curve (1,000 iterations)



Given the uncertainty in the underlying analysis vs. dupilumab, limited sensitivity analyses are provided below in Table 83.

Table 83. Sensitivity analyses for the comparison with roflumilast

Parameter	Scenario	Incr. QALYs	Incr. costs	Deterministic ICER	Rationale
Exploratory analysis	**N/A**	[redacted]	[redacted]	£60,121	**N/A**
Annual probability of discontinuation: First 52 weeks	70%	[redacted]	[redacted]	£48,476	Real world evidence
	20.7%	[redacted]	[redacted]	£62,745	Section B.2.9 suggests discontinuation odds ratio vs. dupilumab is 0.45 (calculated 9.3% / 0.45 = 20.7%)
	100% (All patients discontinue within 1 year)	[redacted]	[redacted]	£42,598	Assumption
Annual probability of discontinuation: beyond 52 weeks	95%	[redacted]	[redacted]	£60,827	Conservative assumption that a small proportion of patients persist beyond 2 years
Source for roflumilast exacerbation relative risk	RR vs dupilumab ([redacted]): alternative ITC (‘*By ratio*’ method)	[redacted]	[redacted]	£49,720	Alternative ITC results suggest a directional benefit for dupilumab in the raised blood EOS on triple therapy population
	RR vs dupilumab ([redacted]) alternative ITC (‘*Direct*’ method)	[redacted]	[redacted]	£55,260	
Alternative source for utility	Mapping exercise conducted by Sanofi	[redacted]	[redacted]	£54,432	Use of the base case source for utility (mapped SGRQ data)

EOS = eosinophils; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; LY = life year; N/A = not applicable; QALY = quality-adjusted life year; RR = rate ratio

We have provided an analysis for the comparison vs. roflumilast and tested this in deterministic sensitivity analysis. The probabilistic ICER is £62,959/QALY and the deterministic ICER is £60,121/QALY. Limited sensitivity analyses examining the key inputs which vary between the base case and the comparison with roflumilast range between £26,214/ QALY and £34,037/ QALY.

B.3.12. Subgroup analysis

The NICE scope suggests that there are two key subgroups that are an important for Type 2 inflammation in COPD. These are patients with very high blood EOS counts (≥500 cells/μL) and those with raised FeNO (≥20 ppb). Clinical outcomes in these subgroups are provided in Appendix E. The incremental cost-effectiveness results for these subgroups are provided in Table 84 and

Table 85, respectively, alongside Figure 36 to Figure 39.

Table 84. Incremental cost-effectiveness results for the subgroup with FeNO ≥20 ppb

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Probabilistic analysis							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,408
Background Therapy	[redacted]	[redacted]	[redacted]				
Deterministic analysis							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,949
Background Therapy	[redacted]	[redacted]	[redacted]				

FeNO = fractional exhaled nitric oxide; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Figure 36. Scatter plot for incremental cost-effectiveness for the subgroup with FeNO ≥20 ppb (1,000 iterations)

FeNO = fractional exhaled nitric oxide; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 37. Cost-effectiveness acceptability curve for the subgroup with FeNO ≥20 ppb (1,000 iterations)

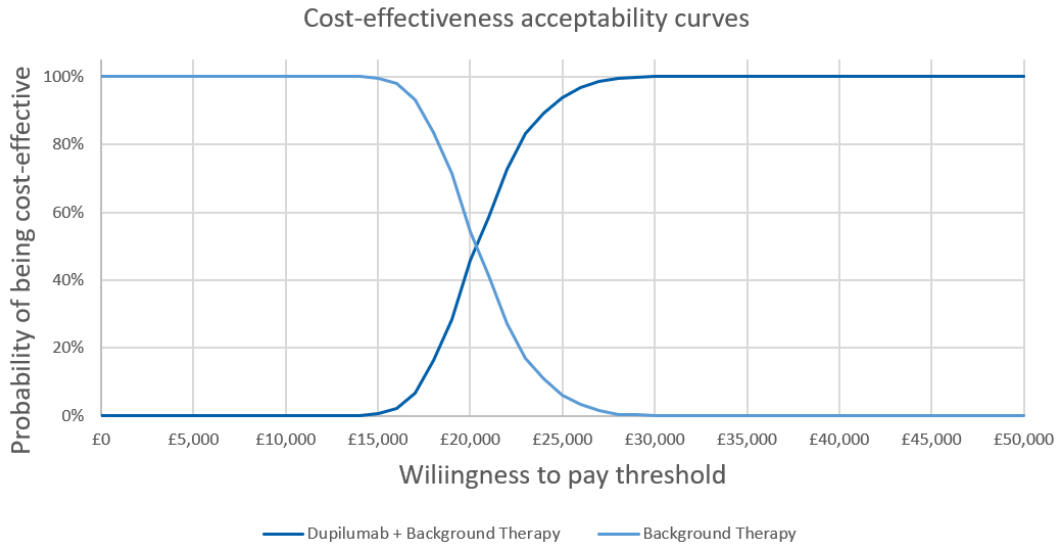


Table 85. Incremental cost-effectiveness results for the subgroup with EOS ≥500 cells/µL

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Probabilistic Analysis							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,286
Background Therapy	[redacted]	[redacted]	[redacted]				
Deterministic analysis							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,721
Background Therapy	[redacted]	[redacted]	[redacted]				

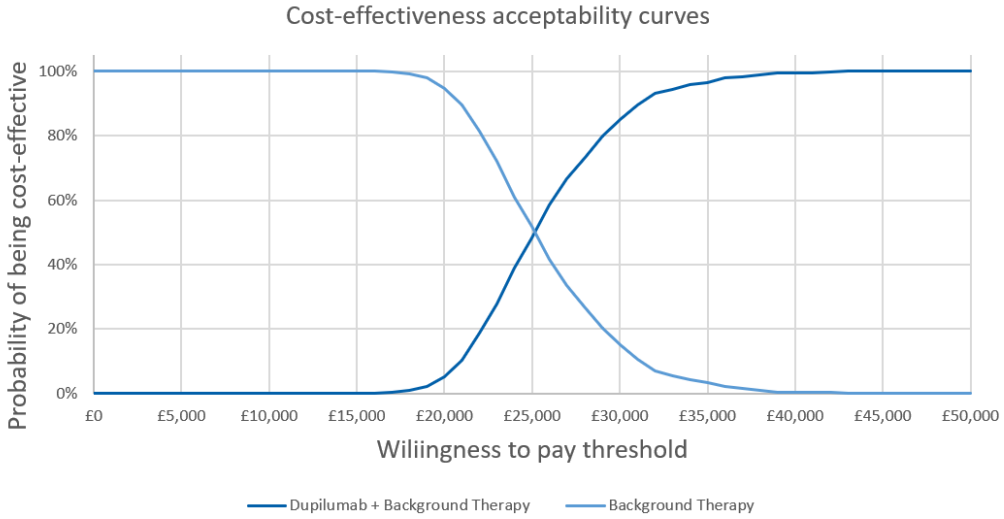
EOS = eosinophils; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Figure 38. Scatter plot for incremental cost-effectiveness for the subgroup with EOS ≥500 cells/µL (1,000 iterations)

[redacted]

EOS = eosinophils; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 39. Cost-effectiveness acceptability curve for the subgroup with EOS ≥500 cells/µL (1,000 iterations)



B.3.13. Benefits not captured in the QALY calculation

Winter pressures on the NHS: People with respiratory disease and COPD in particular, can be significantly affected by cold weather and experience more breathlessness and coughing than usual. This is reflected in the increase in GP visits and hospitalisations during the winter months when there is a 2-fold hazard for exacerbations vs the summer months and the burden on respiratory services in general is at its highest.(125, 250) This is due in part to the increase in circulating respiratory viruses and is a reason that COPD was included in the NHS CORE20PLUS5 initiative to reduce healthcare inequalities at both national and system levels.(23) CORE20PLUS5 focuses on the most deprived 20% of the population amongst whom COPD patients are overrepresented and seeks to increase the uptake of COVID-19, flu, and pneumonia vaccines.(23) Dupilumab also has the potential to relieve some of this healthcare system pressure through a reduction in symptoms and inpatient admissions for exacerbations. This seasonal, but nonetheless important aspect of potential health system impact is not accounted for in the economic model.

Holistic impact of dupilumab on symptoms: The model is designed to capture a multitude of benefits, such as utility due to COPD severity stages, as well as exacerbations, including short-term disutility and long-term impact of each exacerbation. One of the patient-reported endpoints captured in the BOREAS and NOTUS trials, in addition to the SGRQ outcome, is the E-RS: COPD instrument. BOREAS and NOTUS showed that dupilumab was associated with greater reductions in E-RS: COPD total score than background therapy alone, indicating improvements in the severity of respiratory symptoms in patients receiving dupilumab (Section B.2.6.3.2). However, there is no mapping algorithm available to convert E-RS: COPD scores to EQ-5D. Therefore, this benefit may not have

been fully captured by the model in the same way as the SGRQ outcomes, which can be mapped to EQ-5D.

Environmental impact: The model does not capture the anticipated carbon savings associated with the implementation of dupilumab, nevertheless we believe the environmental impact of medicines is an important topic. The implementation of dupilumab for the treatment of COPD may be carbon neutral or carbon saving through reductions in HCRU because of improved outcomes. The NHS is estimated to produce approximately 4% of annual UK carbon emissions.(251) To mitigate its environmental impact, the NHS has committed to reduce direct carbon emissions to net zero by 2040.(252) In light of this objective, we have conducted a study to compare the carbon impact of dupilumab + background therapy versus background therapy alone for the treatment of COPD in the target population of this submission.

The patient care pathway was mapped across four defined areas (primary care visits, inpatient hospitalisations, rescue packs and consultant outpatient appointments) based on technical guidance by the Sustainable Healthcare Coalition and validated through internal interviews.(253) The expected dupilumab-eligible and accessible population was estimated at 13,826 (Section B.1.3.1.2). The annual number of moderate and severe exacerbations in the background therapy arm was based on Whittaker et al. 2022,(26) with a 34% reduction applied to the dupilumab arm based on the NOTUS study.(169) Emissions for dupilumab and background therapy alone were calculated by a lifecycle assessment approach using factors from Tennison et al. 2021.(251) See Appendix O for detailed methods and results for this study.

The implementation of dupilumab for the treatment of COPD for the likely eligible population resulted in an estimated total annual net carbon savings of 253 kg carbon dioxide equivalent (CO_2e) per patient. These savings were driven by reduced HCRU; in particular, avoided hospitalisations accounted for 308 kg CO_2e annual carbon savings per patient for dupilumab versus background therapy alone. Annual net carbon savings in the total dupilumab target population were estimated at 3.5 kilotons (kt) CO_2e. This is equivalent to approximately 5,500 return flights from London to New York or the lifecycle carbon footprint of approximately 2 million plastic bags. In terms of the healthcare sector, this is equivalent to approximately 30% of the annual fuel consumption of the London Ambulance Fleet Service or the lifecycle carbon footprint of approximately 120,000 metered dose inhalers.

B.3.14. Validation

B.3.14.1. Internal validity

A technical model validation was conducted to evaluate the validity of the model programming and sources used to derive input parameters in the model adaptation. The technical validation examines the extent to which mathematical calculations in the model are performed correctly and evaluates their

consistency with the model's specifications. The following steps were performed to ensure the model's technical validity:

1. Extreme-value testing: Each model parameter was set to extremely low and high values to identify any inconsistencies in model behaviour or unexpected results.
2. Technical review (internal): The model programming was reviewed by a senior modeller who was not part of the project team. The technical review process included using different model settings to ensure that they yielded expected calculations. The validator also checked the links between worksheets to ensure that the correct cells were referenced. In addition, mathematical formulae, and the sequence of calculations for each parameter and the model engine were checked.
3. Technical review (external): Further technical review of the final model was conducted by a third party agency who provide additional technical expertise.(254) Some minor issues were identified along with one major issue.(254) These are documented in the validation report (provided in the reference pack) and evidence for the resolution of the issues is provided.(254)
4. Input verification: Values for all parameters were reviewed against source documents, and the inconsistencies were corrected.

Following the validation process, errors identified by the validator were corrected, and the revised model was rechecked by the internal validator.

An additional validation of the model structure and inputs was also performed as part of the advisory board that was held in July 2024 with five experienced UK clinical experts (including respiratory physicians and experts in respiratory epidemiology and respiratory medicine) and two health economists.(167)

B.3.14.2. External validity

In addition to the technical validation of the formulae to ensure correctness, the cost-effectiveness model was also subject to external validation, by comparing the model structure and outcomes to published cost-effectiveness models to achieve face validity (Table 86). There are no previously published cost-effectiveness models evaluating the use of add-on dupilumab therapy in patients with COPD, however; the cost-effectiveness of background therapy (LAMA+LABA, ICS+LAMA+LABA) has been studied in multiple economic models, as summarised below.

Table 86. Summary of external cost-effectiveness models used for validation

Parameter	Fenwick(192)	Trigueros(193)	Hoogendorn(194)	Current CEM	Notes
Settings					

Parameter	Fenwick(192)	Trigueros(193)	Hoogendorn(194)	Current CEM	Notes
Model Structure	Cohort Markov model				There are economic models with other structures which were not considered as a part of external validation
Health states	Stratified based on exacerbation severity and COPD stage				Current CEM also considers sub-states based on the number of exacerbations, as the number of recent exacerbations affect future exacerbations.
Treatment	FF/UMEC/VI (Triple therapy) vs BUD/FOR (Double therapy)	BUD/GLY/FOR (Triple therapy) vs ICS+LABA vs LAMA+LABA	ICS/LABA for 50% of patients	Dupilumab + triple therapy vs triple therapy	The current CEM is flexible to consider a weighted combination of triple and double therapy as background treatment. The base case however considers triple therapy.
Patient characteristics	Based on FULFIL trial; Starting Age = 63.4	Based on ETHOS trial; Starting Age = 64.7	COPD population (N=321,000) in Netherlands (2007). Mean age = 69	BOREAS+NOTUS population. Starting age = 65	Models are largely comparable in terms of population.
Model horizon	Lifetime	Lifetime	10 years	Lifetime	
Health outcomes of background therapy					
Comparator arm used for validation	Triple therapy	Triple therapy	ICS/LABA for 50% of patients (N=113,783)	Triple therapy	Since there is no CEM evaluating dupilumab in COPD patients, the outcomes of background therapy across the models were compared.
LYs	9.094	10.32	Incremental LYs = 0.26 vs reference treatment[†]	Background therapy = [redacted]	
QALYs	6.638	7.55	QALYs gained = 23,800	Background therapy = [redacted]	
Number of moderate exacerbations	5.793	NA	NA	Background therapy = [redacted]	

Parameter	Fenwick(192)	Trigueros(193)	Hoogendorn(194)	Current CEM	Notes
Number of severe exacerbations	1.422	NA	NA	Background therapy = [redacted]	
Number of total exacerbations	7.215	12.8	Exacerbations avoided = 77,000	Background therapy = [redacted]	

BUD = budesonide; CEM = cost-effectiveness model; COPD = Chronic Obstructive Pulmonary Disease; FF = fluticasone furoate; FOR = formoterol; GLY = glycopyrronium; ICS = inhaled corticosteroids; LABA = long-acting beta agonists; LAMA = long-acting muscarinic receptor antagonists; LY = life year; NA = not available; QALY = quality-adjusted life year; UMEC = umeclidinium; VI = vilanterol
† Reference treatment = community-based rehabilitation programme for 15% of patients with moderate-severe COPD
NOTE: There were other published cost-effectiveness models that used a different structure such as the discrete-event simulation model which are not used for external validation.

The health outcomes of the three published cost-effectiveness models that employed a Markov structure were compared against the current model. In addition to health outcomes, the model structures were also compared. All the models utilised health states based on COPD stages, as well as a patient's exacerbation status indicating the importance of both the parameters in the COPD prognosis of a patient, although there was difference in how it was employed. For example, existing models (Fenwick et al(192), Trigueros et al(193)) distinguished based on the presence or absence of recent exacerbations (moderate and severe) whereas the current model goes a step further and also splits patients based on the number of recent exacerbations, in addition to exacerbation type (moderate or severe). However, even though there are differences in the models in terms of structure, the motivation is consistent across approaches to capture the effect of both FEV_1 decline and exacerbation history of COPD patients.

In terms of health outcomes, the Hoogendorn et al. study was not used as it evaluated different treatment strategies for a COPD population (ICS+LABA for 50% of patients vs community-based rehabilitation for 15% of patients).(194) Thus, the outcomes of the other two models(192, 193) which evaluated triple therapy, were used as benchmarks against the current model's triple therapy arm. Based on Table 86, it is evident that the current model's health outcomes, in terms of LYs and QALYs, are lower than those of published models, which is attributable to our ≥300 cells/μL blood eosinophil count (Type 2 inflammation) patient population. There are deviations when it comes to the number of exacerbations amongst external studies, as Fenwick et al.(192) reported a total exacerbation of 7.22 vs. Trigueros et al.(193) which reported a total exacerbation of 12.8. The reasons behind this are not clear, but it could be due to the differences in clinical inputs (exacerbation rates) across the two models. Even though caution must be exercised while comparing the current model's outcomes vs. other models due to differences in structure, clinical inputs, patient population, and other potential factors, the fact that major outcomes are largely comparable between the background therapy arm of the current model vs. precedent models provides a reasonable degree of external validation.

B.3.15. Interpretation and conclusions of economic evidence

Our cost-effectiveness analysis demonstrates that dupilumab represents good value for the NHS as a treatment for patients with uncontrolled COPD (≥2 moderate or ≥1 severe historical exacerbations within 12 months) with raised EOS (≥300 cells/μL).

At the patient access scheme price, add-on treatment with dupilumab results in higher LYs ([redacted]) and QALYs ([redacted]) compared with background therapy alone but is more expensive ([redacted]) due to the higher acquisition cost of dupilumab. Dupilumab + background therapy generates a probabilistic ICER/QALY of £25,793, which is below the commonly accepted WTP threshold of £30,000/QALY. The ICER was consistent when tested against a range of key model inputs and assumptions with very few incremental ICERs rising above £30,000/QALY in extreme scenarios. The model results were primarily driven by discontinuation rate, reference exacerbation rate at baseline, duration of lung function benefit post study, mortality and exacerbation risk.

B.3.15.1. Strengths of the cost-effectiveness analysis

The BOREAS and NOTUS clinical trials were large robust, duplicate studies which provided strong evidence of a significant treatment effect for dupilumab (the first licensed COPD biologic) as add-on to maximal inhaled therapy in patients with uncontrolled COPD (≥2 moderate or ≥1 severe historical exacerbations within 12 months) with raised EOS (≥300 cells/μL). This has not been demonstrated before. A key feature of the studies was the close representation of current clinical practice in COPD as defined by various clinical guidelines (use of triple inhaled therapy [LABA + LAMA + ICS] or double therapy [LABA + LAMA] where ICS is not appropriate). To make best use of all the clinical data in the economic model, we have used the pooled ITT data for our analyses.

Our CEM is designed based on careful consideration of the clinical characteristics and treatment pathway of patients with uncontrolled COPD with raised EOS to ensure that key aspects of the disease and English treatment practices are captured.

Additional strengths of our CEM include:

- The modelling approach, structure, expressions, formulae, sequences of calculations and model inputs were validated by the team who conceptualised and implemented the model, and by a senior reviewer not involved in the project.
- The model employed the state transition approach based on percent predicted FEV_1 (defined by GOLD severity stage) as a measure of disease progression, which is a common approach taken by most of the published COPD models to date. Overall, the current base case results in terms of LYs, QALYs and number of exacerbations based on trial data are comparable to those from the prior models including background therapy.

B.3.15.2. Limitations of the cost-effectiveness analysis

Treatment effect is limited to trial duration of 52 weeks

The follow-up period of the BOREAS and NOTUS trials extends to 52 weeks, therefore whether the benefit of dupilumab can be maintained over the long run is uncertain. We have tested this in terms of FEV_1 treatment effect in a sensitivity analysis. The model has been developed to assess how those clinical benefits observed within the 52-week trial period can potentially transfer into meaningful economic value over an extended time horizon. For example, the model base case utilises a proxy measure from the TRAVERSE study in asthma which shows that lung function benefit was maintained for two years following exit from the RCTs (which lasted 1 year).

Dynamic relationship between exacerbations and disease progression

One of the challenges is the difficulty of capturing the dynamic relationship between exacerbations and disease progression in a transparent and straightforwardly executable economic model. Similar to previous COPD models, the current model considered the number and severity of exacerbations to be dependent on GOLD severity stage but not vice versa, due to the limitations of a conventional Markov structure. As with most newly approved therapies, especially those indicated for chronic disease, there is uncertainty around the extrapolation of trial data beyond the follow-up period of the trial, which affects the validity and applicability of the long-term outcomes. For example, there are limited data on the long-term treatment effect of dupilumab as the first biologic agent to be used for treatment of moderate-to-severe COPD. External data and assumptions are applied for long-term prediction. Sensitivity and scenario analyses have been conducted to examine the uncertainty around these inputs.

Efficacy inputs stratified by GOLD severity could not be obtained directly from the trial

Particularly for mild and very severe COPD stages, the efficacy inputs stratified by GOLD severity stages could not be obtained from the trials due to the small sample sizes; reasonable assumptions have been made to alleviate this issue.

Exacerbation rates by GOLD severity and prior exacerbation status could not be obtained directly from the trial

Adjusted rates were used based on Whittaker et al. 2022, using data from the CPRD database.(26) These published data are further stratified by patients with EOS ≥300 cells/µL which allows for better alignment with the target population of this submission.

B.3.15.3. Generalisability to clinical practice in England

The base case population reflects the anticipated place in therapy for dupilumab in England and is driven by the epidemiology for England and clinical evidence presented in Section B.1 and Section

B.2 alongside English real-world evidence where appropriate. The patient population in the BOREAS and NOTUS trials included in the economic analysis is generalisable to the patient population expected to be treated with dupilumab in English clinical practice and the study comparator of triple therapy makes a within-trial comparison for the economic assessment the most appropriate analysis.

The cost-effectiveness analysis shows that, in addition to treatment effect, baseline exacerbation rates and excess mortality rates due to exacerbations are model drivers. These factors may significantly vary in local clinical practice.

The model structure and approaches for the current analysis are designed to not only closely reflect the clinical outcomes observed in the BOREAS and NOTUS trials but also provide maximum flexibility to use external data where applicable. This allows the generalisability to clinical practice to be assessed in cases where real world data may differ substantially from the BOREAS and NOTUS trials. Despite the challenges and limitations of developing a model that addresses the challenges associated with replicating the complex natural history of COPD, the submitted model sufficiently describes the disease to enable the value of dupilumab from both the healthcare and societal perspectives to be assessed, based on the available evidence and data.

B.3.15.4. Conclusion

The burden of COPD is considerable; medically, socially and economically. Furthermore, as a progressive disease, unfortunately the ultimate outcome for patients with COPD is one of debilitating and disabling symptoms, social isolation and premature death. Sadly, COPD remains one of the leading causes of death in England and worldwide. There is no cure for COPD and few new treatment options have been developed over the last 10-15 years. A large proportion of COPD patients continue to exacerbate and experience debilitating symptoms and poor HRQoL despite maximal inhaled triple therapy. These patients are at high risk of disease progression and death.

The sequalae of COPD are driven by underlying chronic inflammation, and Type 2 inflammation specifically is associated with a poorer prognosis. Type 2 inflammation (defined by blood EOS ≥300 cells/µL) can be targeted with dupilumab, and in two phase III studies, BOREAS and NOTUS, dupilumab has been proven to be effective at significantly reducing the risk of exacerbations (by 31% in the annualised rate of moderate or severe exacerbations, pooled ITT) and improving lung function (73ml in pre-BD FEV_1 compared to background therapy alone, pooled ITT), symptoms and HRQoL, for patients with few further therapeutic options. These results were consistent across the 52 week treatment period.

There are currently 1 million patients treated with dupilumab worldwide and this has enabled Sanofi to establish the strong benefit-risk profile for the product, validated by many clinical trials and further supported by real-world safety data across multiple indications.(182) No new safety signals have been identified in patients with COPD. Dupilumab addresses the high unmet need for a targeted,

systemic biologic treatment for patients with uncontrolled COPD (≥2 moderate or ≥1 severe historical exacerbations within 12 months) and Type 2 inflammation (blood EOS ≥300 cells/μL).

The economic cost of COPD is large, both societally and in terms of medical management. Our health economic modelling indicates that dupilumab is a cost-effective treatment for uncontrolled COPD with Type 2 inflammation as an add-on to background therapy in the NHS. In our base case, we have estimated that the probabilistic ICER is £25,793, which is below the commonly accepted WTP threshold of £30,000. The ICER results were consistent when tested against a range of key model inputs and assumptions with very few incremental ICERs rising above £30,000/QALY in extreme scenarios.

Dupilumab has the potential to generate a significant step-change in the effective treatment of uncontrolled COPD with Type 2 inflammation, providing meaningful benefits to a burdened patient population. Dupilumab also has the potential to relieve pressure on the healthcare system through a reduction in inpatient admissions, particularly in the winter months when most exacerbations occur and the burden on respiratory services is at its highest.

Dupilumab is currently reimbursed in Germany for the treatment of COPD, and on 24 September 2024 the German public radio and television broadcaster, Norddeutscher Rundfunk (NDR), released a video (not commissioned by Sanofi/Regeneron) which amongst other elements captured the experience of a COPD patient while on treatment with dupilumab:(186)

> ***"After 4 days, I recognised an improvement. I could again dress up in the morning, I could take a shower, I could walk again, which was an experience I haven't had in the last year. It's amazing, simply amazing."*** *(Translated German patient testimonial)*

References

1. Sanofi. Dupixent (dupilumab) 300 mg solution for injection in pre-filled pen SmPC - MHRA. Sept 2024.
2. Sanofi. Dupixent (dupilumab) 300 mg solution for injection in pre-filled syringe SmPC - MHRA. Sept 2024.
3. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease 2024 [Available from: https://goldcopd.org/2024-gold-report/.
4. Albert RK, Connett J, Bailey WC, Casaburi R, Cooper JA, Jr., Criner GJ, et al. Azithromycin for prevention of exacerbations of COPD. N Engl J Med. 2011;365(8):689-98.
5. Han MK, Tayob N, Murray S, Dransfield MT, Washko G, Scanlon PD, et al. Predictors of chronic obstructive pulmonary disease exacerbation reduction in response to daily azithromycin therapy. Am J Respir Crit Care Med. 2014;189(12):1503-8.
6. Teva. Azithromycin Summary of Product Characteristics. 2024.
7. National Institute for Health and Care Excellence. Chronic obstructive pulmonary disease in over 16s: diagnosis and management. 2018;2024(February 7).
8. BMJ. Chronic obstructive pulmonary disease (COPD) 2024 [Available from: https://bestpractice.bmj.com/topics/en-us/7/management-approach.
9. Uzun S, Djamin RS, Kluytmans JA, Mulder PG, van't Veer NE, Ermens AA, et al. Azithromycin maintenance treatment in patients with frequent exacerbations of chronic obstructive pulmonary disease (COLUMBUS): a randomised, double-blind, placebo-controlled trial. Lancet Respir Med. 2014;2(5):361-8.
10. Berkhof FF, Doornewaard-ten Hertog NE, Uil SM, Kerstjens HA, van den Berg JW. Azithromycin and cough-specific health status in patients with chronic obstructive pulmonary disease and chronic cough: a randomised controlled trial. Respir Res. 2013;14(1):125.
11. Simpson JL, Powell H, Baines KJ, Milne D, Coxson HO, Hansbro PM, Gibson PG. The effect of azithromycin in adults with stable neutrophilic COPD: a double blind randomised, placebo controlled trial. PLoS One. 2014;9(8):e105609.
12. Brill SE, Law M, El-Emir E, Allinson JP, James P, Maddox V, et al. Effects of different antibiotic classes on airway bacteria in stable COPD using culture and molecular techniques: a randomised controlled trial. Thorax. 2015;70(10):930-8.
13. European Medicines Agency (EMA). Azithromycin-containing medicinal products for systemic use - referral 2024 [updated 15 May. Available from: https://www.ema.europa.eu/en/medicines/human/referrals/azithromycin-containing-medicinal-products-systemic-use.
14. UK Health Security Agency. Antibiotic resistant infections and associated deaths increase 2023 [Available from: https://www.gov.uk/government/news/antibiotic-resistant-infections-and-associated-deaths-increase.
15. Office for National Statistics (ONS). Deaths registered in England and Wales. 2023 dataset.
16. Institute for Health Metrics and Evaluation. Health research by location: United Kingdom - England 2021 [Available from: https://www.healthdata.org/research-analysis/health-by-location/profiles/united-kingdom-england.
17. Public Health England. The 2nd Atlas of variation in risk factors and healthcare for respiratory disease in England. 2019 [Available from: https://fingertips.phe.org.uk/profile/atlas-of-variation.
18. World Health Organization. The top 10 causes of death 2020 [Available from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.
19. Stone PW, Osen M, Ellis A, Coaker R, Quint JK. Prevalence of Chronic Obstructive Pulmonary Disease in England from 2000 to 2019. Int J Chron Obstruct Pulmon Dis. 2023;18:1565-74.
20. Department of Health and Social Care. Policy paper - Major conditions strategy: case for change and our strategic framework. 2023.
21. NHS England. NHS Long Term Workforce Plan. 2024.
22. NHS England. RightCare Pathway: COPD. 2017.
23. NHS England. Core20PLUS5 (adults) – an approach to reducing healthcare inequalities. 2024.

24. Stolz D, Mkorombindo T, Schumann DM, Agusti A, Ash SY, Bafadhel M, et al. Towards the elimination of chronic obstructive pulmonary disease: a Lancet Commission. The Lancet. 2022;400(10356):921-72.
25. Bhatt SP. COPD exacerbations: finally, a more than ACCEPTable risk score. The Lancet Respiratory Medicine. 2020;8(10):939-41.
26. Whittaker H, Rubino A, Müllerová H, Morris T, Varghese P, Xu Y, et al. Frequency and Severity of Exacerbations of COPD Associated with Future Risk of Exacerbations and Mortality: A UK Routine Health Care Data Study. Int J Chron Obstruct Pulmon Dis. 2022;17:427-37.
27. Suissa S, Dell'Aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. Thorax. 2012;67(11):957-63.
28. Guo J, Chen Y, Zhang W, Tong S, Dong J. Moderate and severe exacerbations have a significant impact on health-related quality of life, utility, and lung function in patients with chronic obstructive pulmonary disease: A meta-analysis. Int J Surg. 2020;78:28-35.
29. Mullerova H, Marshall J, de Nigris E, Varghese P, Pooley N, Embleton N, et al. Association of COPD exacerbations and acute cardiovascular events: a systematic review and meta-analysis. Ther Adv Respir Dis. 2022;16:17534666221113647.
30. Whittaker H, Rothnie KJ, Quint JK. Cause-specific mortality in COPD subpopulations: a cohort study of 339 647 people in England. Thorax. 2024;79(3):202-8.
31. Hurst JR, Skolnik N, Hansen GJ, Anzueto A, Donaldson GC, Dransfield MT, Varghese P. Understanding the impact of chronic obstructive pulmonary disease exacerbations on patient health and quality of life. European Journal of Internal Medicine. 2020;73:1-6.
32. Franssen FM, Rochester CL. Comorbidities in patients with COPD and pulmonary rehabilitation: do they matter? Eur Respir Rev. 2014;23(131):131-41.
33. Sanofi. [Data on File] COPD Patient Journey Research - August 2023. 2023.
34. Gruenberger JB, Vietri J, Keininger DL, Mahler DA. Greater dyspnea is associated with lower health-related quality of life among European patients with COPD. Int J Chron Obstruct Pulmon Dis. 2017;12:937-44.
35. Miravitlles M, Peña-Longobardo LM, Oliva-Moreno J, Hidalgo-Vega Á. Caregivers' burden in patients with COPD. Int J Chron Obstruct Pulmon Dis. 2015;10:347-56.
36. Asthma + Lung UK. Investing in breath: Measuring the economic cost of asthma and COPD in the UK and identifying ways to reduce it through better diagnosis and care. 2023.
37. Punekar YS, Wurst K, Shukla A. Resource Use and Costs up to Two Years Post Diagnosis Among Newly Diagnosed COPD Patients in the UK Primary Care Setting: A Retrospective Cohort Study. COPD. 2015;12(3):267-75.
38. Merinopoulou E, Raluy-Callado M, Ramagopalan S, MacLachlan S, Khalid JM. COPD exacerbations by disease severity in England. Int J Chron Obstruct Pulmon Dis. 2016;11:697-709.
39. Asthma + Lung UK. Delayed diagnosis and unequal care: The reality for people with chronic obstructive pulmonary disease (COPD) in the UK in 2022. 2022.
40. Halpin DMG, Dransfield MT, Han MK, Jones CE, Kilbride S, Lange P, et al. The effect of exacerbation history on outcomes in the IMPACT trial. Eur Respir J. 2020;55(5).
41. Tan WC, Bourbeau J, Nadeau G, Wang W, Barnes N, Landis SH, et al. High eosinophil counts predict decline in FEV(1): results from the CanCOLD study. Eur Respir J. 2021;57(5).
42. Alcázar-Navarrete B, Díaz-Lopez JM, García-Flores P, Ortega-Antelo M, Aguilar-Cruz I, Ruiz-Rodríguez O, et al. T2 Biomarkers as Predictors of Exacerbations of Chronic Obstructive Pulmonary Disease. Arch Bronconeumol. 2022;58(8):595-600.
43. National Institute for Health and Care Excellence (NICE). Chronic obstructive pulmonary disease: What is the prognosis? 2024 [Available from: https://cks.nice.org.uk/topics/chronic-obstructive-pulmonary-disease/background-information/prognosis/.
44. Barnes PJ. Inflammatory endotypes in COPD. Allergy. 2019;74(7):1249-56.
45. Agustí A, Christenson S, Han M, Singh D. New Frontiers in Chronic Obstructive Pulmonary Disease: Where Are We Heading? EMJ Respiratory. 2022:2-10.
46. Casanova C, Celli BR, de-Torres JP, Martinez-Gonzalez C, Cosio BG, Pinto-Plata V, et al. Prevalence of persistent blood eosinophilia: relation to outcomes in patients with COPD. Eur Respir J. 2017;50(5).

47. Halpin DMG, de Jong HJI, Carter V, Skinner D, Price D. Distribution, Temporal Stability and Appropriateness of Therapy of Patients With COPD in the UK in Relation to GOLD 2019. EClinicalMedicine. 2019;14:32-41.
48. Oshagbemi OA, Burden AM, Braeken DCW, Henskens Y, Wouters EFM, Driessen JHM, et al. Stability of Blood Eosinophils in Patients with Chronic Obstructive Pulmonary Disease and in Control Subjects, and the Impact of Sex, Age, Smoking, and Baseline Counts. Am J Respir Crit Care Med. 2017;195(10):1402-4.
49. Oshagbemi OA, Franssen FME, van Kraaij S, Braeken DCW, Wouters EFM, Maitland-van der Zee AH, et al. Blood Eosinophil Counts, Withdrawal of Inhaled Corticosteroids and Risk of COPD Exacerbations and Mortality in the Clinical Practice Research Datalink (CPRD). Copd. 2019;16(2):152-9.
50. Ajithkumar CS. Peripheral blood eosinophilia in COPD: prevalence and clinical characteristics. Indian Journal of Basic and Applied Medical Research. 2018;7(2):223-8.
51. Garudadri S, Woodruff PG. Targeting Chronic Obstructive Pulmonary Disease Phenotypes, Endotypes, and Biomarkers. Ann Am Thorac Soc. 2018;15(Suppl 4):S234-S8.
52. Higham A, Beech A, Wolosianka S, Jackson N, Long G, Kolsum U, et al. Type 2 inflammation in eosinophilic chronic obstructive pulmonary disease. Allergy. 2021;76(6):1861-4.
53. Fieldes M, Bourguignon C, Assou S, Nasri A, Fort A, Vachier I, et al. Targeted therapy in eosinophilic chronic obstructive pulmonary disease. ERJ Open Res. 2021;7(2).
54. Gandhi NA, Bennett BL, Graham NM, Pirozzi G, Stahl N, Yancopoulos GD. Targeting key proximal drivers of type 2 inflammation in disease. Nat Rev Drug Discov. 2016;15(1):35-50.
55. Lu Z, Huang W, Wang L, Xu N, Ding Q, Cao C. Exhaled nitric oxide in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. Int J Chron Obstruct Pulmon Dis. 2018;13:2695-705.
56. Office for Health Improvement and Disparities. Public health profiles - COPD: QOF prevalence (all ages) 2024 [
57. Sanofi. [Data on File]. Hospital episode statistics for COPD; fiscal year 2022-23. Mat-xu-2403964 (v1.0). 2024.
58. Office for Health Improvement and Disparities. INteractive Health Atlas of Lung conditions in England (INHALE): March 2023 update 2023 [Available from: https://www.gov.uk/government/statistics/interactive-health-atlas-of-lung-conditions-in-england-inhale-march-2023-update/interactive-health-atlas-of-lung-conditions-in-england-inhale-march-2023-update.
59. Sanofi. [Data on File] Real World And Epidemiology Study Report. Healthcare database study to understand COPD patient pathways and outcomes. Date: 14-Aug-2024. 2024.
60. Royal College of Physicians. National Asthma and Chronic Obstructive Pulmonary Disease Audit Programme (NACAP) Clinical Outcomes October 2018-March 2020 Summary Report. 2023 March 2023.
61. Shavelle RM, Paculdo DR, Kush SJ, Mannino DM, Strauss DJ. Life expectancy and years of life lost in chronic obstructive pulmonary disease: findings from the NHANES III Follow-up Study. Int J Chron Obstruct Pulmon Dis. 2009;4:137-48.
62. National Institute for Health and Care Excellence. Briefing paper - Chronic obstructive pulmonary disease (COPD) update. 2015.
63. Office for Health Improvement & Disparities. Interactive Health Atlas of Lung conditions in England (INHALE): November 2021 update 2021 [Available from: https://www.gov.uk/government/statistics/interactive-health-atlas-of-lung-conditions-in-england-inhale-november-2021-update/interactive-health-atlas-of-lung-conditions-in-england-inhale-november-2021-update.
64. Jo YS. Long-Term Outcome of Chronic Obstructive Pulmonary Disease: A Review. Tuberc Respir Dis (Seoul). 2022;85(4):289-301.
65. Fletcher C, Peto R. The natural history of chronic airflow obstruction. Br Med J. 1977;1(6077):1645-8.
66. Leivseth L, Brumpton BM, Nilsen TIL, Mai X-M, Johnsen R, Langhammer A. GOLD classifications and mortality in chronic obstructive pulmonary disease: the HUNT Study, Norway. Thorax. 2013;68(10):914-21.
67. Izquierdo JL, Miravitlles M, Esquinas C, Perez M, Calle M, Lopez Campos JL, et al. Characteristics of COPD Patients Managed in Respiratory Medicine Departments in Spain,

According to GOLD Groups and GesEPOC Clinical Phenotypes. Arch Bronconeumol (Engl Ed). 2018;54(11):559-67.
68. Mullerova H, Lu C, Li H, Tabberer M. Prevalence and burden of breathlessness in patients with chronic obstructive pulmonary disease managed in primary care. PLoS One. 2014;9(1):e85540.
69. National Institute for Health and Care Excellence (NICE). Chronic obstructive pulmonary disease: What are the complications? 2024 [Available from: https://cks.nice.org.uk/topics/chronic-obstructive-pulmonary-disease/background-information/complications/.
70. Chetty U, McLean G, Morrison D, Agur K, Guthrie B, Mercer SW. Chronic obstructive pulmonary disease and comorbidities: a large cross-sectional study in primary care. Br J Gen Pract. 2017;67(658):e321-e8.
71. Almagro P, Soler-Cataluña JJ, Huerta A, González-Segura D, Cosío BG, on behalf of the CSI. Impact of comorbidities in COPD clinical control criteria. The CLAVE study. BMC Pulmonary Medicine. 2024;24(1):6.
72. Glasheen WP, Cordier T, Gumpina R, Haugh G, Davis J, Renda A. Charlson Comorbidity Index: ICD-9 Update and ICD-10 Translation. Am Health Drug Benefits. 2019;12(4):188-97.
73. Hurst JR, Gale CP. MACE in COPD: addressing cardiopulmonary risk. Lancet Respir Med. 2024;12(5):345-8.
74. Curkendall SM, Lanes S, de Luise C, Stang MR, Jones JK, She D, Goehring E, Jr. Chronic obstructive pulmonary disease severity and cardiovascular outcomes. Eur J Epidemiol. 2006;21(11):803-13.
75. Sin DD, Anthonisen NR, Soriano JB, Agusti AG. Mortality in COPD: Role of comorbidities. Eur Respir J. 2006;28(6):1245-57.
76. Wedzicha JA, Seemungal TA. COPD exacerbations: defining their cause and prevention. Lancet. 2007;370(9589):786-96.
77. Tse G, Emmanuel B, Ariti C, Bafadhel M, Papi A, Carter V, et al. A Long-Term Study of Adverse Outcomes Associated With Oral Corticosteroid Use in COPD. Int J Chron Obstruct Pulmon Dis. 2023;18:2565-80.
78. Bogart M, Bangalore M, McMorrow D, Packnett E. BURDEN OF SYSTEMIC CORTICOSTEROID UTILIZATION IN COPD. CHEST. 2021;160(4):A1780.
79. Mannino DM, Higuchi K, Yu TC, Zhou H, Li Y, Tian H, Suh K. Economic Burden of COPD in the Presence of Comorbidities. Chest. 2015;148(1):138-50.
80. Corlateanu A, Covantev S, Mathioudakis AG, Botnaru V, Siafakas N. Prevalence and burden of comorbidities in Chronic Obstructive Pulmonary Disease. Respir Investig. 2016;54(6):387-96.
81. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. Bmj. 2010;340:c2096.
82. Rockenschaub P, Jhass A, Freemantle N, Aryee A, Rafiq M, Hayward A, Shallcross L. Opportunities to reduce antibiotic prescribing for patients with COPD in primary care: a cohort study using electronic health records from the Clinical Practice Research Datalink (CPRD). Journal of antimicrobial chemotherapy. 2020;75(1):243-51.
83. National Institute for Health and Care Excellence (NICE). Chronic obstructive pulmonary disease (acute exacerbation): antimicrobial prescribing 2018 [Available from: https://www.nice.org.uk/guidance/ng114/resources/chronic-obstructive-pulmonary-disease-acute-exacerbation-antimicrobial-prescribing-pdf-66141598418629.
84. Sanofi. [Data on File] Interview with Asthma + Lung UK Respiratory Nurse. 2024.
85. Lokke A, Hilberg O, Lange P, Ibsen R, Stratelis G, de Fine Licht S, Lykkegaard J. Disease Trajectories and Impact of One Moderate Exacerbation in Gold B COPD Patients. Int J Chron Obstruct Pulmon Dis. 2022;17:569-78.
86. Kunisaki KM, Dransfield MT, Anderson JA, Brook RD, Calverley PMA, Celli BR, et al. Exacerbations of chronic obstructive pulmonary disease and cardiac events. A post hoc cohort analysis from the SUMMIT randomized clinical trial. Am J Respir Crit Care Med. 2018;198(1):51-7.
87. Daniels K, Lanes S, Tave A, Pollack MF, Mannino DM, Criner G, et al. Risk of Death and Cardiovascular Events Following an Exacerbation of COPD: The EXACOS-CV US Study. Int J Chron Obstruct Pulmon Dis. 2024;19:225-41.

88. Williams PJ, Cumella A, Philip KEJ, Laverty AA, Hopkinson NS. Smoking and socioeconomic factors linked to acute exacerbations of COPD: analysis from an Asthma + Lung UK survey. BMJ Open Respir Res. 2022;9(1).
89. Miravitlles M, Ribera A. Understanding the impact of symptoms on the burden of COPD. Respiratory research. 2017;18(1):67.
90. Jones PW. Health status and the spiral of decline. Copd. 2009;6(1):59-63.
91. Miravitlles M, Anzueto A, Legnani D, Forstmeier L, Fargel M. Patient's perception of exacerbations of COPD—the PERCEIVE study. Respiratory medicine. 2007;101(3):453-60.
92. Jones SE, Barker RE, Nolan CM, Patel S, Maddocks M, Man WDC. Pulmonary rehabilitation in patients with an acute exacerbation of chronic obstructive pulmonary disease. J Thorac Dis. 2018;10(Suppl 12):S1390-s9.
93. Miravitlles M, Zalacain R, Murio C, Ferrer M, Alvarez-Sala JL, Masa JF, et al. Speed of recovery from acute exacerbations of chronic obstructive pulmonary disease after treatment with antimicrobials : results of a two-year study. Clin Drug Investig. 2003;23(7):439-50.
94. Kessler R, Ståhl E, Vogelmeier C, Haughney J, Trudeau E, Löfdahl CG, Partridge MR. Patient understanding, detection, and experience of COPD exacerbations: an observational, interview-based study. Chest. 2006;130(1):133-42.
95. Zhang Y, Morgan RL, Alonso-Coello P, Wiercioch W, Bała MM, Jaeschke RR, et al. A systematic review of how patients value COPD outcomes. Eur Respir J. 2018;52(1).
96. Yohannes AM, Kaplan A, Hanania NA. Anxiety and depression in chronic obstructive pulmonary disease: recognition and management. Journal of Family Practice. 2018;67(2):S11-S.
97. Maurer J, Rebbapragada V, Borson S, Goldstein R, Kunik ME, Yohannes AM, Hanania NA. Anxiety and depression in COPD: current understanding, unanswered questions, and research needs. Chest. 2008;134(4):43S-56S.
98. Marsh S, Guck TP. Anxiety and depression: easing the burden in COPD patients. J Fam Pract. 2016;65(4):246-56.
99. Tsai T-Y, Livneh H, Lu M-C, Tsai P-Y, Chen P-C, Sung F-C. Increased risk and related factors of depression among patients with COPD: a population-based cohort study. BMC public health. 2013;13:1-7.
100. Eisner MD, Blanc PD, Yelin EH, Katz PP, Sanchez G, Iribarren C, Omachi TA. Influence of anxiety on health outcomes in COPD. Thorax. 2010;65(3):229-34.
101. Pumar MI, Gray CR, Walsh JR, Yang IA, Rolls TA, Ward DL. Anxiety and depression—Important psychological comorbidities of COPD. Journal of thoracic disease. 2014;6(11):1615.
102. Lecheler L, Richter M, Franzen DP, Rampini SK, Cheetham M, Jenewein J, et al. The frequent and underrecognised co-occurrence of acute exacerbated COPD and depression warrants screening: a systematic review. European Respiratory Review. 2017;26(144).
103. Schneider C, Jick SS, Bothner U, Meier CR. COPD and the risk of depression. Chest. 2010;137(2):341-7.
104. Livermore N, Sharpe L, McKenzie D. Panic attacks and panic disorder in chronic obstructive pulmonary disease: a cognitive behavioral perspective. Respiratory medicine. 2010;104(9):1246-53.
105. Willgoss TG, Yohannes AM. Anxiety disorders in patients with COPD: a systematic review. Respiratory care. 2013;58(5):858-66.
106. Miravitlles M, Worth H, Soler Cataluna JJ, Price D, De Benedetto F, Roche N, et al. Observational study to characterise 24-hour COPD symptoms and their relationship with patient-reported outcomes: results from the ASSESS study. Respir Res. 2014;15(1):122.
107. Kunik ME, Roundy K, Veazey C, Souchek J, Richardson P, Wray NP, Stanley MA. Surprisingly high prevalence of anxiety and depression in chronic breathing disorders. Chest. 2005;127(4):1205-11.
108. Biswas D, Mukherjee S, Chakroborty R, Chatterjee S, Rath S, Das R, Begum S. Occurrence of anxiety and depression among stable COPD patients and its impact on functional capability. Journal of Clinical and Diagnostic Research: JCDR. 2017;11(2):OC24.
109. Yohannes AM, Alexopoulos GS. Depression and anxiety in patients with COPD. European Respiratory Review. 2014;23(133):345-9.

110. Atlantis E, Fahey P, Cochrane B, Smith S. Bidirectional associations between clinically relevant depression or anxiety and COPD: a systematic review and meta-analysis. Chest. 2013;144(3):766-77.
111. Rahi MS, Thilagar B, Balaji S, Prabhakaran SY, Mudgal M, Rajoo S, et al. The Impact of Anxiety and Depression in Chronic Obstructive Pulmonary Disease. Advances in Respiratory Medicine. 2023;91(2):123-34.
112. Miravitlles M, Molina J, Quintano JA, Campuzano A, Pérez J, Roncero C, Investigators DS. Factors associated with depression and severe depression in patients with COPD. Respiratory Medicine. 2014;108(11):1615-25.
113. Hong YJ, Kim Y, Moon J-Y, Park S, Lee J-K, Jung K-S, et al. Associations between depression and anxiety index and frequency of acute exacerbation in chronic obstructive pulmonary disease. Therapeutic Advances in Respiratory Disease. 2023;17:17534666231216591.
114. Blakemore A, Dickens C, Guthrie E, Bower P, Kontopantelis E, Afzal C, Coventry PA. Depression and anxiety predict health-related quality of life in chronic obstructive pulmonary disease: systematic review and meta-analysis. International journal of chronic obstructive pulmonary disease. 2014:501-12.
115. Panagioti M, Scott C, Blakemore A, Coventry PA. Overview of the prevalence, impact, and management of depression and anxiety in chronic obstructive pulmonary disease. International journal of chronic obstructive pulmonary disease. 2014:1289-306.
116. Dalal AA, Shah M, Lunacsek O, Hanania NA. Clinical and economic burden of depression/anxiety in chronic obstructive pulmonary disease patients within a managed care population. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2011;8(4):293-9.
117. Papaioannou AI, Bartziokas K, Tsikrika S, Karakontaki F, Kastanakis E, Banya W, et al. The impact of depressive symptoms on recovery and outcome of hospitalised COPD exacerbations. European Respiratory Journal. 2013;41(4):815-23.
118. Ding B, Judge D, Small M, Bent-Ennakhil N, Siddiqui S. Functional performance in patients with COPD: association with treatment regimen, GOLD group, lung function, and symptom burden in a cross-sectional study. Int J Chron Obstruct Pulmon Dis. 2018;13:2785-96.
119. Gautun H, Werner A, Luras H. Care challenges for informal caregivers of chronically ill lung patients: results from a questionnaire survey. Scand J Public Health. 2012;40(1):18-24.
120. Royal College of General Practioners (RCGP). Managing malnutrition in COPD. Including a pathway for the appropriate use of ONS to support community healthcare professionals. 2016.
121. CancerResearchUK. Lung cancer UK price tag eclipses the cost of any other cancer 2012 [updated 07 Nov. Available from: https://news.cancerresearchuk.org/2012/11/07/lung-cancer-uk-price-tag-eclipses-the-cost-of-any-other-cancer/.
122. Luckett T, San Martin A, Currow DC, Johnson MJ, Barnes-Harris MM, Phillips JL. A systematic review and meta-analysis of studies comparing burden from lung cancer and chronic obstructive pulmonary disease. Palliat Med. 2020;34(10):1291-304.
123. Sanofi. [Data on File] Pathway Burden Analysis in COPD. 2024 Sep.
124. National Asthma and Chronic Obstructive Pulmonary Disease Audit Programme (NACAP). Clinical outcomes. October 2018 – March 2020. Summary report. 2023.
125. Wise RA, Calverley PM, Carter K, Clerisme-Beaty E, Metzdorf N, Anzueto A. Seasonal variations in exacerbations and deaths in patients with COPD during the TIOSPIR(®) trial. Int J Chron Obstruct Pulmon Dis. 2018;13:605-16.
126. Ortega H, Llanos JP, Lafeuille MH, Germain G, Duh MS, Bell CF, et al. Burden of disease associated with a COPD eosinophilic phenotype. Int J Chron Obstruct Pulmon Dis. 2018;13:2425-33.
127. Belanger M, Couillard S, Courteau J, Larivee P, Poder TG, Carrier N, et al. Eosinophil counts in first COPD hospitalizations: a comparison of health service utilization. Int J Chron Obstruct Pulmon Dis. 2018;13:3045-54.
128. Foo J, Landis SH, Maskell J, Oh YM, van der Molen T, Han MK, et al. Continuing to Confront COPD International Patient Survey: Economic Impact of COPD in 12 Countries. PLoS One. 2016;11(4):e0152618.
129. Wacker ME, Jörres RA, Schulz H, Heinrich J, Karrasch S, Karch A, et al. Direct and indirect costs of COPD and its comorbidities: Results from the German COSYCONET study. Respir Med. 2016;111:39-46.

130. NHS England. The NHS Long Term Plan. 2019.
131. National Institute for Health and Care Excellence (NICE). Chronic obstructive pulmonary disease: Goals 2024 [Available from: https://cks.nice.org.uk/topics/chronic-obstructive-pulmonary-disease/goals-outcome-measures/goals/.
132. National Institute for Health and Care Research (NIHR). People with COPD exacerbations prefer early discharge then treatment at home. Lungs and Airways 11.12.18 doi: 10.3310/signal-000691. Available at: https://evidence.nihr.ac.uk/alert/people-with-copd-exacerbations-prefer-early-discharge-then-treatment-at-home/. 2018.
133. National Institute for Health and Care Excellence. Roflumilast for treating chronic obstructive pulmonary disease - Technology appraisal guidance (TA461). 2017.
134. Chong J, Leung B, Poole P. Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2013(11):Cd002309.
135. Rabe KF, Calverley PMA, Martinez FJ, Fabbri LM. Effect of roflumilast in patients with severe COPD and a history of hospitalisation. European Respiratory Journal. 2017;50(1):1700158.
136. Martinez FJ, Calverley PM, Goehring UM, Brose M, Fabbri LM, Rabe KF. Effect of roflumilast on exacerbations in patients with severe chronic obstructive pulmonary disease uncontrolled by combination therapy (REACT): a multicentre randomised controlled trial. Lancet. 2015;385(9971):857-66.
137. Martinez FJ, Rabe KF, Sethi S, Pizzichini E, McIvor A, Anzueto A, et al. Effect of Roflumilast and Inhaled Corticosteroid/Long-Acting β2-Agonist on Chronic Obstructive Pulmonary Disease Exacerbations (RE(2)SPOND). A Randomized Clinical Trial. Am J Respir Crit Care Med. 2016;194(5):559-67.
138. Milpharm. Roflumilast Summary of Product Characteristics. 2024.
139. OpenPrescribing. GP prescribing data for roflumilast. Available at: https://openprescribing.net/analyse/#org=CCG&numIds=0303030B0&denom=nothing&selectedTab=summary. 2024.
140. Martinez FJ, Rabe KF, Calverley PMA, Fabbri LM, Sethi S, Pizzichini E, et al. Determinants of Response to Roflumilast in Severe Chronic Obstructive Pulmonary Disease. Pooled Analysis of Two Randomized Trials. Am J Respir Crit Care Med. 2018;198(10):1268-78.
141. Joo H, Han D, Lee JH, Rhee CK. Incidence of Adverse Effects and Discontinuation Rate between Patients Receiving 250 Micrograms and 500 Micrograms of Roflumilast: A Comparative Study. Tuberc Respir Dis (Seoul). 2018;81(4):299-304.
142. Cilli A, Bal H, Gunen H. Efficacy and safety profile of roflumilast in a real-world experience. J Thorac Dis. 2019;11(4):1100-5.
143. Park TS, Kang J, Lee JS, Oh YM, Lee SD, Lee SW. Adherence to roflumilast under dose-escalation strategy in Korean patients with COPD. Int J Chron Obstruct Pulmon Dis. 2019;14:871-9.
144. Salvesen ONU, Davidsen JR, Pottegard A, Henriksen DP. Roflumilast Usage from 2010 to 2016: A Danish Nationwide Drug Utilization Study. Basic Clin Pharmacol Toxicol. 2018;123(3):314-9.
145. Munoz-Esquerre M, Diez-Ferrer M, Monton C, Pomares X, Lopez-Sanchez M, Huertas D, et al. Roflumilast added to triple therapy in patients with severe COPD: a real life study. Pulm Pharmacol Ther. 2015;30:16-21.
146. Albrecht I, Schild M, Greulich T, et al. Clinical and Economic Burden of COPD in Patients Poorly Controlled on LABA/LAMA or Inhaled Triple Therapy in Germany - A Retrospective Claims Data Analysis (abstract). Am J Respir Crit Care Med 2024;209:A3803. .
147. MHRA. Roflumilast (Daxas▼): risk of suicidal behaviour 2014 [updated 11 December. Available from: https://www.gov.uk/drug-safety-update/roflumilast-daxas-risk-of-suicidal-behaviour.
148. Ji Z, de Miguel-Díez J, Castro-Riera CR, Bellón-Cano JM, Gallo-González V, Girón-Matute WI, et al. Differences in the Outcome of Patients with COPD according to Body Mass Index. J Clin Med. 2020;9(3).
149. National Institute for Health and Care Excellence (NICE). Chronic obstructive pulmonary disease: Scenario: Stable chronic obstructive pulmonary disease 2024 [Available from: https://cks.nice.org.uk/topics/chronic-obstructive-pulmonary-disease/management/stable-copd/.

150. National Institute for Health and Care Excellence (NICE). Chronic obstructive pulmonary disease: Antibiotics 2024 [Available from: https://cks.nice.org.uk/topics/chronic-obstructive-pulmonary-disease/prescribing-information/antibiotics/.
151. Lu Y, Wang X, Zhao J. Effects of azithromycin on treating chronic obstructive pulmonary disease with acute exacerbation of chronic bronchitis in the stable phase. American Journal of Translational Research. 2021;13(6):7370.
152. King PT, MacDonald M, Bardin PG. Bacteria in COPD; their potential role and treatment. Translational respiratory medicine. 2013;1:1-9.
153. Blasi F, Bonardi D, Aliberti S, Tarsia P, Confalonieri M, Amir O, et al. Long-term azithromycin use in patients with chronic obstructive pulmonary disease and tracheostomy. Pulmonary pharmacology & therapeutics. 2010;23(3):200-7.
154. Kanoh S, Rubin BK. Mechanisms of action and clinical application of macrolides as immunomodulatory medications. Clinical microbiology reviews. 2010;23(3):590-615.
155. Li H, Liu DH, Chen LL, Zhao Q, Yu YZ, Ding JJ, et al. Meta-analysis of the adverse effects of long-term azithromycin use in patients with chronic lung diseases. Antimicrob Agents Chemother. 2014;58(1):511-7.
156. Talman S, Uzun S, Djamin RS, Baart SJ, Grootenboers M, Aerts J, van der Eerden M. Long-Term Azithromycin Maintenance Treatment in Patients with Frequent Exacerbations of Chronic Obstructive Pulmonary Disease. Int J Chron Obstruct Pulmon Dis. 2021;16:495-8.
157. Public Health England. Guidance. Health matters: antimicrobial resistance 2015 [updated Dec. Available from: https://www.gov.uk/government/publications/health-matters-antimicrobial-resistance/health-matters-antimicrobial-resistance.
158. Serisier DJ. Risks of population antimicrobial resistance associated with chronic macrolide use for inflammatory airway diseases. Lancet Respir Med. 2013;1(3):262-74.
159. National Institute for Health and Care Excellence (NICE). NICE guideline [NG15]. Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use. 2015.
160. National Institute for Health and Care Excellence (NICE). Quality standard [QS121]. Antimicrobial stewardship. 2016.
161. Chen S, Miravitlles M, Rhee CK, Pavord ID, Jones R, Carter V, et al. Patients with Chronic Obstructive Pulmonary Disease and Evidence of Eosinophilic Inflammation Experience Exacerbations Despite Receiving Maximal Inhaled Maintenance Therapy. Int J Chron Obstruct Pulmon Dis. 2022;17:2187-200.
162. Office for National Statistics (ONS). Inequalities in mortality involving common physical health conditions, England: 21 March 2021 to 31 January 2023. 2023.
163. Office for Health Improvement and Disparities. Public health profiles by deprivation deciles 2024 [Available from: https://fingertips.phe.org.uk.
164. Martin A, Badrick E, Mathur R, Hull S. Effect of ethnicity on the prevalence, severity, and management of COPD in general practice. Br J Gen Pract. 2012;62(595):e76-81.
165. Sanofi. This World COPD Day, let's focus on closing the respiratory inequality gap, and #BreatheEqual 2023 [Available from: https://www.sanofi.co.uk/en/news/2023/world-copd-day.
166. Francis A, Cumella A, editors. Unmet need and barriers in provision of pulmonary rehabilitation for people with COPD: findings from a large UK survey. ERS; 2023.
167. Sanofi. [Data on File] Dupilumab COPD NICE HTA Advisory Board Meeting Report, Date: 12 – 19 July 2024. 2024.
168. Bhatt SP, Rabe KF, Hanania NA, Vogelmeier CF, Cole J, Bafadhel M, et al. Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts. N Engl J Med. 2023;389(3):205-14.
169. Bhatt SP, Rabe KF, Hanania NA, Vogelmeier CF, Bafadhel M, Christenson SA, et al. Dupilumab for COPD with Blood Eosinophil Evidence of Type 2 Inflammation. N Engl J Med. 2024.
170. Sanofi. [Data on File] CSR: A randomized, double-blind, placebo-controlled, parallelgroup, 52-week pivotal study to assess the efficacy, safety, and tolerability of dupilumab in patients with moderate-tosevere chronic obstructive pulmonary disease (COPD) with type 2 inflammation (BOREAS). 2023 August, 8.
171. Sanofi. [Data on File] CSR: 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). 2023 December 14,.
172. Sanofi. [Data on File] SAP: 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). 2023 October 30,.
173. Sanofi. [Data on File] Amended Clinical trial protocol 03: 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). 2023 August 29,.
174. Sanofi. [Data on File] Summary of Clinical Efficacy (Chronic Obstructive Pulmonary Disease). 2023 December 18.
175. Sun C-Y, Tesfaigzi Y, Lee G-Y, Chen Y-H, Weiss ST, Sheng-Kai Ma K. Clinical Effectiveness and Safety of Dupilumab in Chronic Obstructive Pulmonary Disease Patients: A 7-Year Population-based Cohort Study. Journal of Allergy and Clinical Immunology. 2024.
176. Sanofi. [Data on File] Statistical Analysis Plan for Summary of Clinical Efficacy: 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. 2023 October 30,.
177. Sanofi. [Data on File] Summary of Clinical Safety (Chronic Obstructive Pulmonary Disease). 2023 December 19.
178. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
179. Sanofi. [Data on File] COPD ISE Appendix. 2023 December 18.
180. de la Loge C, Tugaut B, Fofana F, Lambert J, Hennig M, Tschiesner U, et al. Relationship Between FEV(1) and Patient-Reported Outcomes Changes: Results of a Meta-Analysis of Randomized Trials in Stable COPD. Chronic Obstr Pulm Dis. 2016;3(2):519-38.
181. Dias S, Welton NJ, Sutton A, Ades AE. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework For Pairwise And Network Meta-Analysis Of Randomised Controlled Trials. Report By The Decision Support Unit. August 2011 (last updated April 2014). 2014.
182. Sanofi. [Data on File] Periodic benefit risk evaluation report. Dupilumab. Covered period: 29-Mar-2023 to 28-Mar-2024. 2024.
183. Sanofi. Dupixent® late-breaking data from NOTUS confirmatory phase 3 COPD study presented at ATS and published in NEJM [press release] 2024 [updated May 20. Available from: https://www.sanofi.com/assets/dotcom/pressreleases/2024/2024-05-20-18-15-00-2885068-en.pdf.
184. Sanofi. Dupixent approved in the US as the first-ever biologic medicine for patients with COPD 2024 [updated 27 September 2024. Available from: https://www.sanofi.com/en/media-room/press-releases/2024/2024-09-27-13-35-00-2954551.
185. Sanofi. Dupixent (dupilumab) SmPC - MHRA. Feb 2024.
186. Norddeutscher Rundfunk. COPD: Neues Medikament Dupilumab bei schweren Verläufen. Available at: https://www.ndr.de/fernsehen/sendungen/visite/COPD-Neues-Medikament-Dupilumab-bei-schweren-Verlaeufen,visite24060.html. 2024.
187. Starkie HJ, Briggs AH, Chambers MG, Jones P. Predicting EQ-5D values using the SGRQ. Value Health. 2011;14(2):354-60.
188. Jackson D, Jenkins M, de Nigris E, Purkayastha D, Patel M, Ouwens M. Associations between the EQ-5D-5L and exacerbations of chronic obstructive pulmonary disease in the ETHOS trial. Qual Life Res. 2024;33(4):1029-39.
189. National Institute for Health and Care Excellence. Chronic obstructive pulmonary disease in over 16s: diagnosis and management. Economic model report (NICE guideline NG115). 2018.
190. Briggs AH, Baker T, Risebrough NA, Chambers M, Gonzalez-McQuire S, Ismaila AS, et al. Development of the Galaxy Chronic Obstructive Pulmonary Disease (COPD) Model Using Data from ECLIPSE: Internal Validation of a Linked-Equations Cohort Model. Med Decis Making. 2017;37(4):469-80.

191. Hoogendoorn M, Feenstra TL, Asukai Y, Briggs AH, Hansen RN, Leidl R, et al. External Validation of Health Economic Decision Models for Chronic Obstructive Pulmonary Disease (COPD): Report of the Third COPD Modeling Meeting. Value in Health. 2017;20(3):397-403.
192. Fenwick E, Martin A, Schroeder M, Mealing SJ, Solanke O, Risebrough N, Ismaila AS. Cost-effectiveness analysis of a single-inhaler triple therapy for COPD in the UK. ERJ Open Res. 2021;7(1).
193. Trigueros JA, Garin N, Baloira A, Aceituno S, Calvo A, Prades M, et al. Cost-effectiveness analysis of triple therapy with budesonide/glycopyrronium/formoterol fumarate versus dual therapy in patients with chronic obstructive pulmonary disease in Spain. International Journal of Chronic Obstructive Pulmonary Disease. 2022:2905-17.
194. Hoogendoorn M, Rutten-van Mölken MP, Hoogenveen RT, Al MJ, Feenstra TL. Developing and applying a stochastic dynamic population model for chronic obstructive pulmonary disease. Value in health. 2011;14(8):1039-47.
195. Exuzides A, Colby C, Briggs AH, Lomas DA, Rutten-van Molken M, Tabberer M, et al. Statistical Modeling of Disease Progression for Chronic Obstructive Pulmonary Disease Using Data from the ECLIPSE Study. Med Decis Making. 2017;37(4):453-68.
196. Hurst JR, Han MK, Singh B, Sharma S, Kaur G, de Nigris E, et al. Prognostic risk factors for moderate-to-severe exacerbations in patients with chronic obstructive pulmonary disease: a systematic literature review. Respir Res. 2022;23(1):213.
197. Chen H, Luo X, Du Y, He C, Lu Y, Shi Z, Zhou J. Association between chronic obstructive pulmonary disease and cardiovascular disease in adults aged 40 years and above: data from NHANES 2013-2018. BMC Pulm Med. 2023;23(1):318.
198. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual 2022.
199. Anzueto A. Impact of exacerbations on COPD. Eur Respir Rev. 2010;19(116):113-8.
200. Rutten-van Molken M, Lee TA. Economic modeling in chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2006;3(7):630-4.
201. Rutten-van Mölken MP, Hoogendoorn M, Lamers LM. Holistic preferences for 1-year health profiles describing fluctuations in health: the case of chronic obstructive pulmonary disease. Pharmacoeconomics. 2009;27(6):465-77.
202. Zhang S, Wang J, Li X, Zhang H. Comparative effectiveness and safety of triple therapy and non-triple therapy interventions for COPD: an overview of systematic reviews. Ther Adv Respir Dis. 2024;18:17534666241259634.
203. Sanofi. [Data on File] COPD IQVIA Hospital Pharmacy Audit. 2024.
204. Djamin RS, Talman S, Schrauwen EJA, von Wintersdorff CJH, Wolffs PF, Savelkoul PHM, et al. Prevalence and abundance of selected genes conferring macrolide resistance genes in COPD patients during maintenance treatment with azithromycin. Antimicrob Resist Infect Control. 2020;9(1):116.
205. World Health Organization. Model List of Essential Medicines. 23rd list. 2023 [updated 26 Jul. Available from: https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.02.
206. Department of Health & Social Care. Confronting antimicrobial resistance 2024 to 2029. 2024.
207. Sanofi. [Data on File] SAR231893. NOTUS (interim analysis cut-off date: 29SEP2023) & BOREAS (cut-off date: 08FEB2023) – Post-hoc analyses for CE model - ITT population. Date: 29 July 2024. 2024.
208. Wallace AE, Kaila S, Bayer V, Shaikh A, Shinde MU, Willey VJ, et al. Health Care Resource Utilization and Exacerbation Rates in Patients with COPD Stratified by Disease Severity in a Commercially Insured Population. J Manag Care Spec Pharm. 2019;25(2):205-17.
209. Wechsler ME, Ford LB, Maspero JF, Pavord ID, Papi A, Bourdin A, et al. Long-term safety and efficacy of dupilumab in patients with moderate-to-severe asthma (TRAVERSE): an open-label extension study. Lancet Respir Med. 2022;10(1):11-25.
210. Wenzel S, Castro M, Corren J, Maspero J, Wang L, Zhang B, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. The Lancet. 2016;388(10039):31-44.
211. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. New England journal of medicine. 2018;378(26):2486-96.

212. Rabe KF, Nair P, Brusselle G, Maspero JF, Castro M, Sher L, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. New England journal of medicine. 2018;378(26):2475-85.
213. ClinicalTrials.gov. Evaluation of Dupilumab's Effects on Airway Inflammation in Patients With Asthma (EXPEDITION) 2024 [Available from: https://clinicaltrials.gov/study/NCT02573233.
214. National Clinical Guideline Centre. National Institute for Health and Clinical Excellence: Guidance. Chronic Obstructive Pulmonary Disease: Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care. London: Royal College of Physicians (UK) Copyright © 2010, National Clinical Guideline Centre - Acute and Chronic Conditions.; 2010.
215. Quanjer PH, Tammeling G, Cotes J, Pedersen O, Peslin R, Yernault J. Lung volumes and forced ventilatory flows. European respiratory journal. 1993;6(Suppl 16):5-40.
216. Sanofi. [Data on File] Homecare data for dupilumab in asthma. 2024.
217. Suissa S, Dell'Aniello S, Ernst P. Triple Inhaler versus Dual Bronchodilator Therapy in COPD: Real-World Effectiveness on Mortality. Copd. 2022;19(1):1-9.
218. Humenberger M, Horner A, Labek A, Kaiser B, Frechinger R, Brock C, et al. Adherence to inhaled therapy and its impact on chronic obstructive pulmonary disease (COPD). BMC Pulm Med. 2018;18(1):163.
219. Dickens A, Halpin D, Carter V, Skinner D, Beeh K, Chalmers J, et al. S117 Poor adherence in exacerbating COPD patients: magnitude and related factors at baseline in the MAGNIFY pragmatic trial. Thorax. 2022;77(Suppl 1):A72-A3.
220. Mansur AH, Gonem S, Brown T, Burhan H, Chaudhuri R, Dodd JW, et al. Biologic therapy practices in severe asthma; outcomes from the UK Severe Asthma Registry and survey of specialist opinion. Clinical & Experimental Allergy. 2023;53(2):173-85.
221. GBD 2021 Causes of Death Collaborators. Global burden of 288 causes of death and life expectancy decomposition in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet. 2024;403(10440):2100-32.
222. Hoogendoorn M, Hoogenveen RT, Rutten-van Mölken MP, Vestbo J, Feenstra TL. Case fatality of COPD exacerbations: a meta-analysis and statistical modelling approach. Eur Respir J. 2011;37(3):508-15.
223. Office for National Statistics (ONS). National life tables – life expectancy in the UK: 2020 to 2022 2024 [updated January 11. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2020to2022.
224. Connors AF, Jr., Dawson NV, Thomas C, Harrell FE, Jr., Desbiens N, Fulkerson WJ, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). Am J Respir Crit Care Med. 1996;154(4 Pt 1):959-67.
225. Vestbo J, Prescott E, Lange P, Schnohr P, Jensen G. Vital prognosis after hospitalization for COPD: a study of a random population sample. Respir Med. 1998;92(5):772-6.
226. Groenewegen KH, Schols AM, Wouters EF. Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. Chest. 2003;124(2):459-67.
227. Gunen H, Hacievliyagil SS, Kosar F, Mutlu LC, Gulbas G, Pehlivan E, et al. Factors affecting survival of hospitalised patients with COPD. Eur Respir J. 2005;26(2):234-41.
228. McGhan R, Radcliff T, Fish R, Sutherland ER, Welsh C, Make B. Predictors of rehospitalization and death after a severe exacerbation of COPD. Chest. 2007;132(6):1748-55.
229. Brekke PH, Omland T, Holmedal SH, Smith P, Søyseth V. Troponin T elevation and long-term mortality after chronic obstructive pulmonary disease exacerbation. Eur Respir J. 2008;31(3):563-70.
230. Rothnie KJ, Müllerová H, Smeeth L, Quint JK. Natural History of Chronic Obstructive Pulmonary Disease Exacerbations in a General Practice-based Population with Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2018;198(4):464-71.
231. Ståhl E, Lindberg A, Jansson SA, Rönmark E, Svensson K, Andersson F, et al. Health-related quality of life is related to COPD disease severity. Health Qual Life Outcomes. 2005;3:56.

232. Freemantle N, Wilson A, Fisher M. Mapping The St George's Respiratory Questionnaire To The Euroqol 5 Dimensions: A Study In Patients With Idiopathic Pulmonary Fibrosis. Value in Health. 2015;18(7):A503.
233. Hernández Alava M, Wailoo A, Pudney S, Gray L, Manca A. Mapping clinical outcomes to generic preference-based outcome measures: development and comparison of methods. Health Technol Assess. 2020;24(34):1-68.
234. Spencer M, Briggs AH, Grossman RF, Rance L. Development of an economic model to assess the cost effectiveness of treatment interventions for chronic obstructive pulmonary disease. Pharmacoeconomics. 2005;23(6):619-37.
235. Sadatsafavi M, Ghanbarian S, Adibi A, Johnson K, FitzGerald JM, Flanagan W, et al. Development and validation of the Evaluation Platform in COPD (EPIC): a population-based outcomes model of COPD for Canada. Med Decis Making. 2019;39(2):152-67.
236. Hernández Alava M, Pudney S, Wailoo A. Estimating EQ-5D by Age and Sex for the UK. Report by the Decision Support Unit. 2022.
237. Borg S, Ericsson A, Wedzicha J, Gulsvik A, Lundback B, Donaldson GC, Sullivan SD. A computer simulation model of the natural history and economic impact of chronic obstructive pulmonary disease. Value Health. 2004;7(2):153-67.
238. Sterne JA, Bodalia PN, Bryden PA, Davies PA, Lopez-Lopez JA, Okoli GN, et al. Oral anticoagulants for primary prevention, treatment and secondary prevention of venous thromboembolic disease, and for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis and cost-effectiveness analysis. Health Technol Assess. 2017;21(9):1-386.
239. National Institute for Health and Care Excellence (NICE). British National Formulary (BNF). Last updated: 2 October 2024. 2024.
240. Jones K, Weatherly H., Birch S, Castelli A, et al. Unit Costs of Health and Social Care 2023 Manual 2024 [Available from: https://kar.kent.ac.uk/105685/1/The%20unit%20costs%20of%20health%20and%20social%20care_Final3.pdf.
241. Hertel N, Kotchie RW, Samyshkin Y, Radford M, Humphreys S, Jameson K. Cost-effectiveness of available treatment options for patients suffering from severe COPD in the UK: a fully incremental analysis. International journal of chronic obstructive pulmonary disease. 2012:183-99.
242. NHS England. National Schedule of NHS Costs Year 2022/23. National Cost Collection Data Publication.
243. National Health Service. 2010-11 reference costs publication [cited 2011 November 17]. Available from: https://www.gov.uk/government/publications/2010-11-reference-costs-publication.
244. National Institute for Health and Care Excellence (NICE). Scenario: Acute exacerbation of chronic obstructive pulmonary disease 2024 [Available from: https://cks.nice.org.uk/topics/chronic-obstructive-pulmonary-disease/management/acute-exacerbation/.
245. UK National Health Service. 2021/22 National Cost Collection Data Publication: NHS Trusts and NHS Foundation Trust; 2023 [updated May 19, 2023. Available from: https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/.
246. Jansson SA, Backman H, Stenling A, Lindberg A, Rönmark E, Lundbäck B. Health economic costs of COPD in Sweden by disease severity--has it changed during a ten years period? Respir Med. 2013;107(12):1931-8.
247. The Motley Fool. Average Retirement Age in the UK: Statistics for 2022 2022 [Available from: https://www.fool.co.uk/personal-finance/research/average-retirement-age-in-the-uk/.
248. Statista. Employment rate in the United Kingdom from 2nd quarter 1992 to 2nd quarter 2024, by age group 2024 [Available from: https://www.statista.com/statistics/280228/uk-employment-rate-by-age-group/.
249. Forbes. Average UK Salary By Age In 2024 2024 [Available from: https://www.forbes.com/uk/advisor/business/average-uk-salary-by-age/.
250. NHS England. Living with respiratory conditions in cold weather 2013 [Available from: https://www.england.nhs.uk/blog/penny-woods/.

251. Tennison I, Roschnik S, Ashby B, Boyd R, Hamilton I, Oreszczyn T, et al. Health care's response to climate change: a carbon footprint assessment of the NHS in England. Lancet Planet Health. 2021;5(2):e84-e92.
252. NHS England. Delivering a net zero NHS 2024 [Available from: https://www.england.nhs.uk/greenernhs/a-net-zero-nhs/
253. Coalition for Sustainable Pharmaceuticals and Medical Devices. Care Pathways: Guidance on Appraising Sustainability. 2015 Oct.
254. Sanofi. [Data on File] York Health Economics Consortium (YHEC) Model Technical Validation Report. 2024.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Dupilumab for treating moderate to severe chronic obstructive pulmonary disease [ID6235]

Summary of Information for Patients (SIP)

File name	Version	Contains confidential information	Date
ID6235_Dupilumab_SIP_30102024_noACIC	Final	No	30 October 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article.

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: Dupilumab

Brand name: DUPIXENT®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Adults with uncontrolled chronic obstructive pulmonary disease (COPD) and Type 2 inflammation on triple inhaled therapy (inhaled corticosteroid [ICS], long-acting beta2-agonist [LABA] and long-acting muscarinic antagonist [LAMA]) or double inhaled therapy (LABA and LAMA) if ICS is not appropriate.

"Uncontrolled COPD" means that the person experienced two or more moderate exacerbations (those requiring treatment with corticosteroids or antibiotics) or one or more severe exacerbations (those requiring hospitalisation) in the last year.

"Type 2 inflammation" means that the person has raised numbers of immune cells called eosinophils in the blood (≥300 cells per µL).

Note that dupilumab treatment is not indicated for all people with COPD, only those fulfilling the specific licenced criteria (as described above).

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Dupilumab was authorised for the treatment of adults with uncontrolled COPD with raised blood eosinophils on triple inhaled therapy (or double inhaled therapy if ICS are not appropriate) by the UK regulator, the Medicines and Healthcare products Regulatory Agency (MHRA), on 9 September 2024.(1, 2)

In the UK, dupilumab has also been authorised by the MHRA for the following indications:(1, 2)

Atopic dermatitis (eczema)

Adults and adolescents: Dupixent is indicated for the treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy.

Children 6 months to 11 years of age: Dupixent is indicated for the treatment of severe atopic dermatitis in children 6 months to 11 years old who are candidates for systemic therapy.

Asthma

Adults and adolescents: Dupixent is indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with Type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO), who are inadequately controlled with high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment.

Children 6 to 11 years of age: Dupixent is indicated in children 6 to 11 years old as add-on maintenance treatment for severe asthma with Type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with medium to high dose ICS plus another medicinal product for maintenance treatment.

Chronic rhinosinusitis with nasal polyposis (CRSwNP)

Dupixent is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.

Prurigo Nodularis (PN)

Dupixent is indicated for the treatment of adults with moderate to severe PN, who are candidates for systemic therapy.

Eosinophilic esophagitis (EoE)

Dupixent is indicated for the treatment of eosinophilic oesophagitis in adults and adolescents 12 years and older, weighing at least 40 kg, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Transfers of value between Sanofi UK and the relevant organisations in the United Kingdom are outlined below. For ease of reading, all engagements are disclosed in the format of: “Project title, amount. Disclosure statement.”

2024

- Financial support for the Taskforce for Lung Health organised by Asthma + Lung UK. £55,000. Sanofi has provided financial support to the Taskforce for Lung Health and is thereby a member of its Industry Forum. Industry proposals are subject to healthcare professional review.
- Asthma + Lung UK representative attending Global Patient Community Council. £80.00. [travel costs only] Sanofi has engaged Asthma + Lung UK on a zero-fee basis (in accordance with the organisation’s corporate engagement policy) to attend its Global Patient Community Council.

- Attending roundtable on improving access to innovative medicines for people with COPD. £00.00. Sanofi has engaged Asthma + Lung UK on a zero-fee basis (in accordance with the organisation's corporate engagement policy) to attend an above-brand roundtable on improving access to innovative medicines for people with COPD.
- COPD Roadshow Partnership Agreement. £90,000. Sanofi has engaged Asthma + Lung UK in a partnership agreement involving use of Asthma + Lung UK branding, provision of Asthma + Lung UK speakers, and consultancy on materials for the COPD Roadshow.
- Representative of Asthma + Lung UK attending a COPD advisory board. £0.00. Sanofi has engaged a representative of Asthma + Lung UK on a zero-fee basis (in accordance with the organisation's corporate engagement policy) to attend an advisory board on COPD.
- Sanofi has engaged Asthma + Lung UK on a zero-fee basis (in accordance with the organisation's corporate engagement policy) for their CEO to speak at a Sanofi-led Parliamentary event in November 2024.

2023

- Taskforce for Lung Health 2023. £25,000. Sanofi UK has provided a financial contribution to the Asthma UK and British Lung Foundation Partnership for implementation of the Taskforce of the Lung Health.
- Filmed discussion on health inequalities. £0.00. Sanofi has engaged Asthma + Lung UK on a zero-fee basis (in accordance with the organisation's corporate engagement policy) for its Director of External Affairs to participate in the filming of a discussion amongst experts on health in asthma inequalities.
- South Asian Health Foundation (SAHF) patient introduction services. £520.00. Sanofi engaged SAHF in a fee for service to identify and introduce people in their network living with atopic dermatitis to participate in a medical photography project.

2022

Financial contribution to the Taskforce for Lung Health (Asthma UK – British Lung Foundation) Partnership. £25,000. Sanofi UK has provided a financial contribution to the Asthma UK and British Lung Foundation Partnership for implementation of the Taskforce of the Lung Health.

2021

Asthma UK and British Lung Foundation Partnership (precursor organisation to Asthma + Lung UK). £25,000. Sanofi UK has made a financial contribution to the Asthma UK and British Lung Foundation Partnership towards the cost of running the Task force for Lung Health.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

COPD is a long-term condition affecting the airway and lungs.(3) In people with COPD, the airways become narrowed and the small air sacs in the lungs responsible for passing oxygen to the blood become damaged.(3) This leads to breathing difficulties, including feeling breathless when carrying out everyday activities (referred to as dyspnoea), persistent coughing (often with phlegm) and wheezing.(3) People with COPD experience episodes of sudden worsening of these symptoms, called exacerbations or lung attacks.(4) COPD exacerbations cause further damage to the lungs and often result in the person needing to go to hospital for treatment as well as increase the risk of having more exacerbations in the future.(5-8) In some cases, COPD exacerbations can be fatal.(9) People with more severe COPD (i.e., those with worse symptoms and/or more frequent exacerbations) are more likely to die from their disease.(9, 10)

What causes COPD?

COPD is caused by long-term inflammation in the airway and lungs, which results in narrowing of the airways, overproduction of phlegm (mucous) and damage to the small air sacs in the lungs responsible for passing oxygen to the blood.(4, 11) Inflammation in COPD leads to an increase in the number of immune cells in the blood and in the lungs.(4, 11) There are two types of inflammation in COPD, depending on the type of immune cells involved: Type 1 (which leads to an increase in immune cells called neutrophils) and Type 2 (which leads to an increase in immune cells called eosinophils).(12, 13) Up to 40% of people with COPD have Type 2 inflammation, which is the focus of this submission.(14-18)

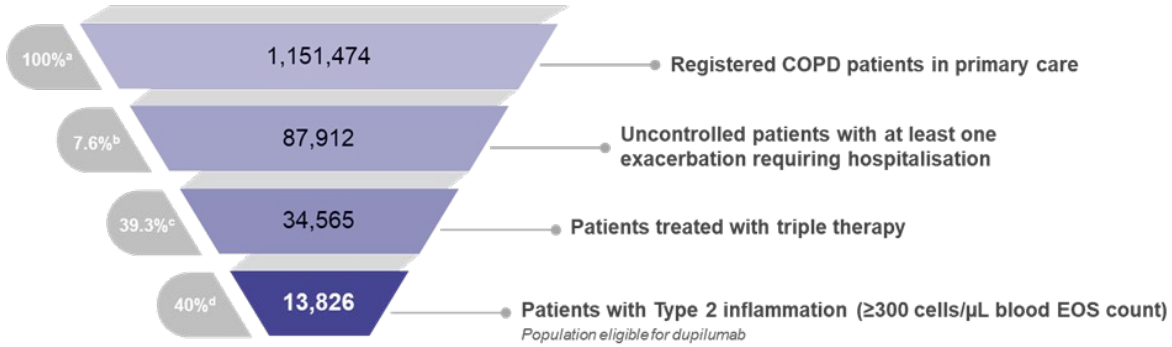
What are the risk factors for COPD?

The main risk factor for developing COPD is breathing in harmful substances over a long period of time, such as tobacco smoke, air pollution, or dust or fumes at work.(4) People are also more likely to develop COPD as they get older or if they had chest problems as a child.(4)

How many people are living with COPD in England?

As of 2022/2023, 1,151,474 people were living with COPD in England.(19) Of these, approximately 14,000 are expected to be eligible for treatment with dupilumab. This estimate was determined using the approach summarised in Figure 1.

Figure 1. Number of people with COPD in England eligible for treatment with dupilumab



COPD = chronic obstructive pulmonary disease; EOS = eosinophil; HES = Hospital Episode Statistics; QoF = Quality and Outcomes Framework
[a]Based on QoF England (2022/2023)(19); [b]Based on HES England data (2022/2023)(20); [c]Based on Whittaker et al. 2022(5); [d]Based on published literature.(14-18)

COPD and life expectancy

COPD is a leading cause of death in England and around the world – in 2021 it was estimated that 21,701 people died from COPD in England alone.(21-23) In addition, death rates for people with lung disease (including COPD) are 61% higher in the UK compared to the rest of Europe.(24) The life expectancy of current or former smokers with COPD in England is up to 6 years shorter than that of the general population (in addition to being ~3.5 years shorter already due to smoking).(25)

What is the impact of COPD on a person's quality of life?

Sanofi interviewed 8 people living with COPD in the UK in 2023 to understand their experience of the condition.(26) Participants reported feelings of shame and stigma from having COPD, which impacts hugely on every aspect of their life.(26) For many, life feels extremely limited and they are frequently confined to their homes.(26) People with COPD feel there is little that can be done to improve their quality of life.(26) One person surveyed said *"There's nothing they can give me. I'm basically stuck with it….I just have to live with it, it's just the way it is".*(26)

COPD affects all aspects of a person's life, including their ability to perform routine tasks, physical impairments, quality of sleep and overall wellbeing.(27, 28) People with COPD are also more likely to suffer from depression or anxiety, even in comparison to people with other long-term diseases such as cancer or diabetes.(29-31) This further reduces their quality of life and can also make their COPD worse.(32-34) People with more severe COPD (i.e., those with poor lung function, worse symptoms or who experience more exacerbations) experience the greatest reductions to their quality of life.(35, 36)

COPD also affects people's ability to work. A survey in the UK found that 52% of people with COPD reported being completely unable to work, while 18% reported having a reduced ability to work.(37) People with COPD may also have to retire earlier from work due to their disease than those without COPD.(38)

What is the impact of COPD on caregivers?

Most people with COPD require support from informal caregivers, such as a family member or friend.(39) Caregivers are often physically, emotionally and financially impacted, which can have significant negative effects on their daily lives.(40) Caregivers of people with COPD experience a level of burden similar to that of caregivers of people with other chronic diseases, such as stroke or cancer.(40)

What is the economic cost of COPD to patients, caregivers and the NHS?

COPD is associated with considerable healthcare resource utilisation (HCRU) and associated direct costs, as well as high indirect costs due to absenteeism, reduced productivity and early retirement among people with COPD and caregivers. For example:

- A cost of illness model developed by Asthma + Lung UK estimated that the total cost of COPD in England, including both direct and indirect costs, was £7.9 billion in 2023.(41)
- In the UK, 70% of people with COPD report that the condition has a negative impact on their work, reducing their ability to work or leaving them unable to work at all.(37)

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

It can often take many years for a person to be correctly diagnosed with COPD.(4, 38) In a survey conducted by Asthma + Lung UK in 2022, 1 in 8 people with COPD had to wait 10 or more years for a diagnosis.(38)

The clinician will initially assess the person's symptoms and history. They will ask if the person experiences persistent breathlessness (dyspnoea) that is worse with exercise, regular wheezing and/or coughing (with phlegm), or frequent lower respiratory tract infections.(4, 42) They will also ask about risk factors for COPD, such as work history and whether they have ever smoked.(4, 42)

To confirm if a person has COPD, the clinician will ask them to perform a simple test called spirometry.(4, 42) This involves blowing air hard and fast into a machine in order to measure the total amount of air the person can breathe out and how quickly they can empty their lungs.(43) A healthy person can usually breathe out 70% or more of the air in their lungs within one second.(43) If spirometry shows that the person can breathe out less than this, the clinician may diagnose COPD.(4)

The clinician may further classify the person's COPD based on their symptoms and exacerbations.(4, 42) People with COPD are classified into one of three lettered groups (A, B or E).(4) People in group E have more frequent exacerbations, and broadly represent the focus of this submission.(4)

Dupilumab treatment is not indicated for all people with COPD, only those fulfilling the specific licenced criteria. Dupilumab is licenced in the UK for adults with uncontrolled COPD and Type 2 inflammation (raised blood eosinophils) on triple inhaled therapy (or double therapy if ICS aren't appropriate).(1, 2) COPD is considered "uncontrolled" if the person experiences two or more moderate exacerbations (those requiring treatment with corticosteroids or antibiotics) or one or more severe exacerbations (those requiring hospitalisation) in the last year. Type 2 inflammation can be detected through a simple blood test to count the number of eosinophils in the blood.(4) If eosinophil levels are over 300 cells/μL, this will be classified as Type 2 inflammation and the person may be considered eligible for treatment with dupilumab.

2c) Current treatment options

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

All people with COPD are encouraged to stop smoking and take additional steps (such as exercise, coping strategies and ensuring vaccinations are up to date) to improve their lung function and overall health.(42) People may additionally be referred for pulmonary rehabilitation. These are part of the five 'fundamentals of care' for people with COPD, laid out in the NICE guidelines.(42)

Inhaled therapies are recommended for people with COPD who have tried the above strategies but continue to experience breathlessness and exercise limitation.(42)

As a first step, the NICE 2019 guidelines recommend inhaled therapies such as short-acting β2 antagonists (SABAs) and short-acting muscarinic antagonists (SAMAs).(42) For people who continue to experience symptoms and exacerbations on these treatments, the NICE 2019 guidelines recommend double therapy (a combination of a LABA + LAMA or a LABA + ICS) and then escalate to triple therapy (LABA + LAMA + ICS) if symptoms or exacerbations persist.(42)

For people whose COPD is not controlled on triple therapy (or double therapy if ICS aren't appropriate), the NICE 2019 guidelines recommend add-on treatment with azithromycin for non-smokers or roflumilast for people with severe COPD and chronic bronchitis (swelling and irritation of the airways).(42)

However, azithromycin is not licenced for use in COPD, requires additional testing prior to prescription and monitoring, and carries the risk of severe adverse events (AEs) such as hearing loss and irregular heart rhythm, as well as developing antibiotic resistance.(44, 45) Roflumilast is associated with gastrointestinal side effects as well as insomnia, depressive mood symptoms and risk of suicidal behaviour, and up to two-thirds of people stop treatment in real-world practice.(46-50)

Market research conducted by Sanofi in the UK in 2023 has shown that clinicians perceive current treatment options beyond triple therapy to be very limited.(26) **There are currently no therapies specifically recommended for people with uncontrolled COPD and Type 2 inflammation (raised blood eosinophils) in England.** It is anticipated that dupilumab will be used as add-on to triple therapy (or double therapy if ICS aren't appropriate) in people with uncontrolled COPD (experiencing frequent exacerbations) and Type 2 inflammation (raised blood eosinophils).

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Market research conducted by Sanofi in August 2023 among people with COPD (n=8) and clinicians (n=12) in the UK reinforces that COPD is a condition characterised by despair.(26) Most people with COPD surveyed had been hospitalised at least once, and all but one were using triple therapy.(26) All people with COPD surveyed were regularly using oral steroids and/or antibiotics to manage exacerbations.(26)

In the survey, people with COPD reported that COPD feels like a very frightening, long, protracted death sentence which they have brought upon themselves.(26) This leads to shame and stigma, and impacts hugely on every aspect of their life.(26) For many, life feels extremely limited and they are frequently confined to their homes.(26) People with COPD feel there is little that can be done to improve their HRQoL.(26) One person surveyed said "*There's nothing they can give me. I'm basically stuck with it….I just have to live with it, it's just the way it is*".(26)

The clinicians surveyed also recognised that there is little they can achieve, as current treatments, which have remained unchanged over the past decades, have limited impact.(26) Their main goal is to stabilise the person's condition, which, despite their efforts, will ultimately progress, placing an emotional burden on healthcare professionals (HCPs).(26) The clinicians surveyed reported that they find it difficult, if not impossible, to break the cycle of exacerbations and associated hospitalisations for some people with COPD and this can ultimately lead to a sense of failure.(26) A respiratory specialist stated that "*The despair is the patients, but also that translates to the doctor. It's not curable and they endlessly come back …(and) there is only so much we can do*".(26)

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a Summary of Product Characteristics or patient information leaflet, please provide a link to these.

As described in Section 2a, up to 40% of people with COPD have Type 2 inflammation, which is identified by increased numbers of eosinophils in the blood.(13-18) Two key chemical signals in the lung, called interleukin-4 and interleukin-13 (IL-4 and IL-13), are responsible for Type 2 inflammation and the resulting damage to the airway and lungs that occurs in COPD.(11, 51-53)

Dupilumab is a recombinant human monoclonal antibody that blocks IL-4 and IL-13 from signalling.(1, 2) Blocking IL-4/IL-13 signalling with dupilumab reduces Type 2 inflammation and the resulting damage to the airway and lungs.(1, 2)

Dupilumab is an innovative treatment for COPD as it is the only targeted therapy for people with uncontrolled COPD and Type 2 inflammation despite maximal inhaled therapy. Furthermore, dupilumab can be prescribed without conducting any additional safety testing, and requires no routine monitoring beyond what would be expected for COPD.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes/No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Yes. It is anticipated that dupilumab will be used as add-on to triple therapy (or double therapy if ICS is not considered appropriate) in people with uncontrolled COPD and Type 2 inflammation (raised blood eosinophils).

People who receive dupilumab for COPD are expected to have already received, and to continue receiving, triple therapy (or double therapy if ICS aren't appropriate).

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Dupilumab is intended to be prescribed at all UK specialised centres. These centres currently prescribe dupilumab for conditions like severe asthma and moderate to severe atopic dermatitis (eczema).

The recommended dose of dupilumab for adults with COPD is 300 mg given every other week (once every 2 weeks).(1, 2) Dupilumab can be self-administered or administered by a carer or healthcare professional.(1, 2) It is administered by subcutaneous injection (into the layer of fatty tissue immediately under the skin) in the thigh or abdomen, except for 5 cm around the navel, using a single-use pre-filled syringe or pen.(1, 2) If the injection is being administered by somebody else, the upper arm can also be used.(1, 2)

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The clinical efficacy and safety of dupilumab for the treatment of COPD has been studied in two phase 3 randomised clinical trials, BOREAS (NCT03930732) and NOTUS (NCT04456673).

People enrolled in the BOREAS and NOTUS trials had uncontrolled COPD (frequent exacerbations) and evidence of Type 2 inflammation (raised blood eosinophils) whilst on background inhaled therapy (triple therapy or double therapy if ICS wasn't considered appropriate).(54, 55)

Both BOREAS and NOTUS primarily looked at how adding dupilumab to background therapy reduced people's annual rate of moderate or severe COPD exacerbations over 52 weeks, compared to the annual rates of people who had been randomly allocated to receive placebo in addition to background therapy.(54, 55)

Both BOREAS and NOTUS were phase 3, placebo-controlled, double blind, randomised trials.(54, 55) Double blinding means that both the people enrolled in the trial and the healthcare professionals involved do not know which people have been randomised to receive either dupilumab or placebo.(56)

- **BOREAS**(54) – Completed 8 February 2023
    - The BOREAS trial was conducted in 275 sites across 24 countries worldwide.
    - People who could participate were adults aged ≥40 to ≤80 years with a diagnosis of moderate to severe COPD and high blood eosinophil count with documented history of high exacerbation risk when receiving background triple therapy for 3 months (or double if ICS aren't appropriate).
    - A total of 939 people with COPD were enrolled and randomised to receive dupilumab (468 people) or placebo (471 people), with continued background therapy.
- **NOTUS**(55, 57, 58) – Completed 28 February 2024
    - The NOTUS trial was conducted in 329 sites across 29 countries worldwide, including the UK. NOTUS enrolled 12 people from 11 sites in England.
    - People who could participate were adults aged ≥40 to ≤85 years with a diagnosis of moderate to severe COPD and high blood eosinophil count with documented history of high exacerbation risk when receiving background triple therapy for 3 months (or double if ICS was not considered appropriate).
    - A total of 935 people with COPD were enrolled and randomised to receive dupilumab (470 people) or placebo (465 people), with continued background therapy.

Currently there are no other ongoing studies of dupilumab for people with COPD.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

In both the BOREAS and NOTUS trials, treatment with dupilumab significantly reduced the annual number of moderate to severe exacerbations compared to placebo in people whose COPD was not controlled despite background therapy.(58) When the results of the two trials were analysed together ("pooled"), people receiving dupilumab had 31% fewer moderate to severe exacerbations over 52 weeks compared to people receiving placebo.(54, 58)

Dupilumab also led to early and sustained improvements in lung function compared to placebo.(58) In the “pooled” analysis, people receiving dupilumab had greater lung function improvements (as measured by pre-BD FEV_1) than people receiving placebo, when assessed at Week 12 (improvement: +83 ml).(58)

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease-specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

In the BOREAS and NOTUS trials, the quality of life of participants was assessed using the St. George’s Respiratory Questionnaire (SGRQ) with total scores ranging from 0 (better) to 100 (worse) and an established minimum clinically important difference (MCID) of ≥4 or more points.(54, 55)

Dupilumab resulted in early and sustained improvements in quality of life at Week 52 compared to placebo.(54, 55, 58) When the results of the two trials were analysed together (“pooled”), dupilumab resulted in a greater reduction (improvement) in SGRQ total score at Week 52 compared to placebo (improvement: −3.4).(58)

More people in the dupilumab group achieved a clinically meaningful improvement in quality of life compared to placebo.(58) A higher proportion of participants in the dupilumab arm achieved a clinically meaningful improvement (reduction by ≥4 or more points) in SGRQ total score than in the placebo arm (51.4% vs. 44.6%).(58)

In the BOREAS and NOTUS trials, the severity of respiratory symptoms was assessed using the Evaluating Respiratory Symptoms in COPD (E-RS: COPD) scale, with total scores ranging from 0 (less severe) to 40 (more severe).(54, 55) The E-RS: COPD total score measures three aspects of respiratory symptoms in COPD: breathlessness, cough and phlegm, and chest symptoms.(59)

Dupilumab led to early and sustained improvements in respiratory symptoms at 52 weeks compared to placebo.(58) Dupilumab resulted in a greater reduction (improvement) in E-RS: COPD total score compared to placebo at Week 52 (improvement: −0.9).(58)

Dupilumab is currently available in Germany for the treatment of COPD and, on 24 September 2024, a German public radio and television broadcaster released a video (not commissioned by Sanofi/Regeneron) which captured the experience of a person with COPD who was being treated with dupilumab:(60)

“After 4 days, I recognised an improvement. I could again dress up in the morning, I could take a shower, I could walk again, which was an experience I haven’t had in the last year. It’s amazing, simply amazing.” *(Translated German patient testimonial)*

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Dupilumab is an established treatment for multiple diseases and has been used in England since 2018. To date, over 1 million people have been treated with dupilumab across multiple licenced indications worldwide.(61)

In BOREAS and NOTUS, dupilumab demonstrated a favourable safety and tolerability profile in adults with uncontrolled COPD and evidence of Type 2 inflammation whilst on background therapy.(54, 55)

Treatment-emergent adverse events (TEAEs) are safety events recorded in clinical trials arising during the course of treatment. They may be, or may not be, associated with or caused by the treatment (dupilumab add-on to background therapy, or placebo add-on to background therapy).

When the results of the two clinical trials were analysed together ("pooled"):(62)

- The proportion of participants with TEAEs was similar with dupilumab (72.1%) and placebo (71.0%).
- The most common TEAEs in the dupilumab group (with a difference to the placebo group) were headache (7.8% vs. 6.6%), back pain (4.5% vs. 3.1%), urinary tract infection (3.0% vs. 1.9%) and gastritis (2.0% vs. 0.7%).
- The most common TEAEs in the placebo group (with a difference to the dupilumab group) were COPD (6.9% vs. 5.3%) and hypertension (4.6% vs. 3.4%).
- Treatment-emergent severe adverse events (SAEs) were reported in 125 (13.3%) participants in the dupilumab group and 147 (15.7%) participants in the placebo group.
- 3.4% of participants receiving dupilumab had to stop treatment due to a TEAE, compared to 3.0% of participants receiving placebo.

As dupilumab is already approved and used for several other conditions (e.g., atopic dermatitis, asthma and chronic rhinosinusitis with nasal polyps), its safety profile is well understood and has been established in several other clinical trials including over 15,000 participants.(63)

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration.

There are currently no therapies specifically recommended for people with uncontrolled COPD and Type 2 inflammation in England. Dupilumab has an established safety profile and will be the first therapy for COPD that specifically targets chemical signals (IL-4 and

IL-13) in the inflammatory pathway, thereby reducing Type 2 inflammation and the resulting damage to the airways and lungs.(1, 2, 54, 55)

In BOREAS and NOTUS, people treated with dupilumab experienced fewer moderate to severe exacerbations, improved lung function, less severe symptoms and better quality of life compared to those receiving placebo (see Sections 3d to 3g for additional information about the clinical efficacy and safety outcomes).(54, 55) Dupilumab also demonstrated a favourable safety and tolerability profile, in people with COPD and other diseases.

The improvements in exacerbations, lung function and symptoms seen with dupilumab have the potential to reduce the risk of people dying from their COPD.(9, 10) Reductions in the number of moderate to severe exacerbations experienced by people treated with dupilumab also have the potential to reduce the risk of future exacerbations as well as the number of times a person needs to visit hospital.(5-9)

Improvements in exacerbations and symptoms may allow people with COPD to continue their normal daily activities for longer as well as improve their overall wellbeing.(27) Symptoms of anxiety and depression may improve as COPD symptoms are reduced and thereby enable people with COPD to better perform self-care and increase physical activity.(64)

Improved symptoms and quality of life may enable people with COPD and their caregivers, who might otherwise be forced to reduce their workload or retire early, to continue working and avoid any loss of income due to their disease.(38, 40, 41, 65-67)

People are able to self-administer dupilumab (or have a caregiver help with administration) through a simple injection every other week.(1, 2) No additional tests or monitoring beyond those already recommended for people with COPD are required.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

People with COPD may need to travel to their nearest secondary care centre for their first consultation with a specialist to access dupilumab add-on therapy, which may be a challenge for some people (see Section 3l). Dupilumab is self-administered via subcutaneous injection into the thigh or abdomen, except for 5 cm around the navel, using a single-use pre-filled syringe or pen.(1, 2) Administration via injection may be unpleasant to people who experience a fear of needles or prefer other modes of administration, such as oral pills or inhalation.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Health economic modelling

Sanofi has submitted a health economic model for evaluation by NICE. The following sections describe how the model was structured and how it attempts to reflect the reflect the progression of COPD over time.

What is the structure of the model?

The model starts with a close description of the trial period by using a 'decision tree', in which people with COPD are allocated to dupilumab or background therapy, as occurred during the clinical trials BOREAS and NOTUS. This is a common way of modelling the trial period. For each treatment, people are assigned to one of four groups based on how severe their disease is (mild, moderate, severe or very severe based on their lung function). At the end of the decision tree, outcomes for the people taking dupilumab are assessed and, if they have more exacerbations than they did in the year before taking dupilumab, their treatment is stopped and they revert back to what they were taking before. This rule is put in place in the model to ensure that the NHS doesn't continue to spend money and resources on treating people who would not benefit.

After the decision tree, people then move to the longer-term part of the model that uses the clinical trial results to predict the difference between what would happen if people were treated with dupilumab plus background therapy compared to what would happen if they only received background therapy. During this part of the model, the impact of dupilumab treatment on exacerbations and lung function is considered as well as how treatment influences disease progression over time. This includes exacerbations.

Does the treatment extend life?

The trials for dupilumab were 52 weeks long so they were not able to show that dupilumab could extend life because this is too short a time to observe a difference in the death rate between dupilumab and background therapy. Worsening lung function and exacerbations are known to lead to shorter survival. Our model suggests that because dupilumab improved lung function in the clinical trials and reduced the number of exacerbations, life may be extended. This includes both the total number of years lived and the number of years lived in better health.

How do trial outcomes feed into the economic model?

The clinical trials collected data on the risk of having exacerbations with dupilumab plus background therapy compared to the risk with background therapy alone. These data are

used in the model to calculate how many exacerbations people have whilst taking each treatment. In addition, the clinical trials recorded how lung function improved with each treatment. This data is included in the model decision tree. In the longer-term part of the model, we assume that lung function gets worse over time, as this is what happens normally when people age. The number of exacerbations a person experiences will affect how quickly their lung function gets worse in this longer-term part of the model.

Which quality of life measures are used to estimate a person's quality of life over time and on treatment?

Quality of life was measured during the clinical trials using the SGRQ (as described in Section 3f). These data have been transformed into 'Utilities' for our model, as this is NICE's preferred measure for quality of life in economic models.

People with more severe COPD (worse lung function) have worse quality of life. Therefore, the model assigns different levels of quality of life (utilities) to each severity group (mild, moderate, severe or very severe; as described above). Each time a person experiences an exacerbation, this leads to a small decrease in quality of life.

Because people experience fewer exacerbations and slower worsening of lung function whilst taking dupilumab, they experience better quality of life in the model (more utilities) than people treated with background therapy alone.

The model doesn't include the negative impact that COPD has on carers or family members (see Section 2a). This may mean that it underestimates the benefit that dupilumab may have.

Modelling how the costs of treatment differ with dupilumab

The model also compares the cost of treating people with dupilumab plus background therapy to background therapy alone. It calculates the differences in the cost of the medicines and the cost of NHS services such as GP appointments or hospital stays.

As would be expected, dupilumab + background therapy is more expensive than background therapy alone, as people are receiving two treatments rather than one. Nevertheless, the cost burden of COPD on patients, their caregivers and the NHS is substantial (Section 2a), and dupilumab has the potential to save money by preventing many of the costs that occur due to disease progression, poor quality of life and early death. This is because treatment with dupilumab leads to:

- Less severe symptoms and better quality of life (Section 3f).(54, 55) This could enable people with COPD and their caregivers, who might otherwise be forced to reduce their workload or retire early, to continue working and avoid any loss of income due to their disease.(38, 40, 41, 65-67)
- Significantly fewer moderate to severe exacerbations and improved lung function (Section 3e).(54, 55) People with less severe COPD (in terms of lung function, symptoms and exacerbations) have fewer GP visits, outpatient visits and hospital admissions, and use their rescue medication less (e.g., oral corticosteroids and antibiotics).(41, 66) By improving lung function, symptoms and exacerbations, dupilumab has the potential to reduce the burden of COPD on the NHS.
- Reduced usage of the antibiotic azithromycin which carries the risk of severe AEs, such as hearing loss and irregular heart rhythm, as well as developing antibiotic resistance. Consequently azithromycin is being reviewed by the European Medicines Agency (EMA) with the aim of restricting its use, and is included in the World Health

Organization's Watch list.(68, 69) Antibiotic resistance and its associated burden remain a key concern of the UK government.(70)

Are there any important differences in the way the medicine is given compared with those already in use that will affect the experience of the patient or costs to the health service or patients (e.g., where it is given or the monitoring that is needed)?

Dupilumab is self-administered every other week (once every two weeks) via a pre-filled syringe or pen, does not place any additional burden on the health service and has favourable safety and tolerability.(1, 2, 71)

Type 2 inflammation can be detected through a simple blood test to count the number of eosinophils in the blood.(4) If eosinophil levels are over 300 cells/μL, this will be classified as Type 2 inflammation and the person may be considered eligible for treatment with dupilumab. Other than testing for Type 2 inflammation, no other tests are required to prescribe dupilumab beyond what is required for routine COPD diagnosis and monitoring.(1, 2) In contrast, other treatments recommended by NICE for uncontrolled COPD require additional testing and/or monitoring:

- Azithromycin requires additional testing prior to prescription (including heart and liver function tests and testing of the person's phlegm to identify the type of bacteria present) as well as ongoing monitoring due to the risk of serious adverse effects.(44, 45)
- Roflumilast requires additional testing prior to prescription (including heart and liver function tests) and ongoing monitoring for persistent intolerability and body weight as it causes weight loss;(45, 72) people with COPD who are underweight have a poorer prognosis.(73)

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see Section 3f)

As the first and only licensed therapy which targets underlying Type 2 inflammation in COPD,(1, 2) dupilumab has demonstrated improvements in clinical outcomes and quality of life compared to inhaled therapy for people with COPD whose disease remains uncontrolled despite maximal treatment with inhaled therapy.(1, 2, 54, 55)

Other current treatments recommended for people with uncontrolled COPD despite triple therapy (or double therapy if ICS aren't appropriate) are not targeted, are associated with significant safety concerns and lack specific evidence to support their use in people with uncontrolled COPD and Type 2 inflammation.

BOREAS and NOTUS clinical trials have shown that the use of dupilumab as an add-on to maintenance therapy addresses the current unmet need for a targeted, effective and well-tolerated treatment that can provide significant clinical improvements in terms of exacerbation reduction, lung function, quality of life and symptoms in people with uncontrolled COPD and Type 2 inflammation.(54, 55)

Dupilumab provides people with COPD and clinicians a treatment option that has demonstrated efficacy and a well-established and favourable safety profile.(54, 55) Please see Sections 3d to 3g for additional information about the clinical efficacy and safety outcomes.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
COPD is a debilitating and progressive disease that disproportionately affects people of certain demographics and those living in certain regions of England.(24, 74, 75) People from poorer households are more likely to develop COPD than people from more affluent households.(75) Additionally, the number of deaths due to COPD is higher among people living in more deprived areas, among people who have never worked or are in long-term unemployment, and those living in the North and Northeast of England.(24, 74) People of different ethnicities or socioeconomic status in England may not have access to the same treatments for COPD. Access to pulmonary rehabilitation is lower in the North West than the South East of England, and also among people of Black or South Asian background than those of White background.(76, 77) Additionally, despite advice that use of oral corticosteroids (OCS) should be minimised due to the risks associated with long-term use,(42) prescribing of OCS remains substantially higher in people with COPD or asthma from the most deprived areas than in those from the least deprived areas.(78) The current lack of licenced, reimbursed, effective advanced treatments with a favourable safety profile is already placing people with COPD at a significant disadvantage compared to people with other chronic diseases (e.g., rheumatological and cardiovascular disease and diabetes) who have had access to advanced targeted treatments for several years.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open-access materials or provide copies that patients can access.
• **BOREAS**: Pivotal Study to Assess the Efficacy, Safety and Tolerability of Dupilumab in Patients With Moderate-to-severe COPD With Type 2 Inflammation (BOREAS). Available at: https://clinicaltrials.gov/study/NCT03930732?term=NCT03930732 • **BOREAS**: Bhatt SP, Rabe KF, Hanania NA, Vogelmeier CF, Cole J, Bafadhel M, Christenson SA, Papi A, Singh D, Laws E, Mannent LP, Patel N, Staudinger HW, Yancopoulos GD, Mortensen ER, Akinlade B, Maloney J, Lu X, Bauer D, Bansal A, Robinson LB, Abdulai RM; BOREAS Investigators. Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts. N Engl J Med. 2023 Jul 20;389(3):205-214. doi: 10.1056/NEJMoa2303951. Epub 2023 May 21. PMID: 37272521. Available at: https://www.nejm.org/doi/pdf/10.1056/NEJMoa2303951 • **NOTUS**: Bhatt SP, Rabe KF, Hanania NA, Vogelmeier CF, Cole J, Bafadhel M, Christenson SA, Papi A, Singh D, Laws E, Mannent LP, Patel N, Staudinger HW, Yancopoulos GD, Mortensen ER, Akinlade B, Maloney J, Lu X, Bauer D, Bansal A,

Robinson LB, Abdulai RM; BOREAS Investigators. Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts. N Engl J Med. 2023 Jul 20;389(3):205-214. doi: 10.1056/NEJMoa2303951. Epub 2023 May 21. PMID: 37272521. Available at: https://www.nejm.org/doi/full/10.1056/NEJMoa2401304

- **NOTUS**: Pivotal Study to Assess the Efficacy, Safety and Tolerability of Dupilumab in Patients With Moderate to Severe COPD With Type 2 Inflammation (NOTUS). Available at: https://clinicaltrials.gov/study/NCT04456673?term=NCT04456673
- Asthma + Lung UK: COPD (chronic obstructive pulmonary disease) | Asthma + Lung UK (asthmaandlung.org.uk)

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Adverse event/Side effect: An unexpected medical problem that arises during treatment with a drug or other therapy. Adverse events may be mild, moderate, or severe.

Clinical trial: A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. Also called clinical study.

Dyspnoea: A subjective feeling of breathlessness, shortness of breath and/or uncomfortable breathing.

EMA (European Medicines Agency): The regulatory body that evaluates, approves, and supervises medicines throughout the European Union.

Evaluating Respiratory Symptoms in COPD (E-RS: COPD): COPD scale used to measure the effect of treatment on the severity of respiratory symptoms in stable COPD

Healthcare resource utilisation (HCRU): Refers to the use of healthcare services, such as treatments, GP visits, outpatient hospital visits, hospitalisations, emergency room admissions etc.

HTA (Health Technology Assessment) bodies: Bodies that make recommendations groups regarding the financing and reimbursing of new medicines and medical products based on the added value (efficacy, safety, medical resources saving) of a therapy compared to existing ones.

MHRA (Medicines and Healthcare products Regulatory Agency): The body that regulates medicines, medical devices and blood components for transfusion in the UK.

Pre-BD FEV_1: Refers to the "prebronchodilator forced expiratory volume in 1 second", meaning the volume of air that can be breathed out in the first second of forced exhalation during a spirometry test. The test is performed before a person has used their bronchodilator medication.

Primary endpoint: The outcome measured to answer the key question in a clinical trial.

Quality of life: The overall enjoyment of life. Many clinical trials assess it to measure aspects of an individual's sense of wellbeing and ability to carry out activities of daily living.

Secondary endpoint: An outcome measured to answer an additional question of interest in a clinical trial.

Spirometry: A common lung function test for people with COPD. It measures how much air is breathed in, how much air is breathed out, and how quickly it is breathed out.

St. George's Respiratory Questionnaire (SGRQ): Disease-specific instrument designed to measure impact on overall health, daily life, and perceived wellbeing in people with obstructive airways disease.

Triple therapy: In COPD, triple therapy consists of a LAMA in combination with a LABA and ICS.

Type 2 inflammation: An overactive immune response in which Type 2 immune cells (e.g., eosinophils) are activated even though there is no infection or allergen. As a result, the immune cells end up damaging the body itself and causing inflammation.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. Sanofi. Dupixent (dupilumab) 300 mg solution for injection in pre-filled pen SmPC - MHRA. Sept 2024.
2. Sanofi. Dupixent (dupilumab) 300 mg solution for injection in pre-filled syringe SmPC - MHRA. Sept 2024.
3. Asthma + Lung UK. What is Chronic Obstructive Pulmonary Disease (COPD)? 2022.
4. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease 2024 [Available from: https://goldcopd.org/2024-gold-report/.
5. Whittaker H, Rubino A, Müllerová H, Morris T, Varghese P, Xu Y, et al. Frequency and Severity of Exacerbations of COPD Associated with Future Risk of Exacerbations and Mortality: A UK Routine Health Care Data Study. Int J Chron Obstruct Pulmon Dis. 2022;17:427-37.
6. Suissa S, Dell'Aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. Thorax. 2012;67(11):957-63.
7. Guo J, Chen Y, Zhang W, Tong S, Dong J. Moderate and severe exacerbations have a significant impact on health-related quality of life, utility, and lung function in patients with chronic obstructive pulmonary disease: A meta-analysis. Int J Surg. 2020;78:28-35.
8. Mullerova H, Marshall J, de Nigris E, Varghese P, Pooley N, Embleton N, et al. Association of COPD exacerbations and acute cardiovascular events: a systematic review and meta-analysis. Ther Adv Respir Dis. 2022;16:17534666221113647.
9. Whittaker H, Rothnie KJ, Quint JK. Cause-specific mortality in COPD subpopulations: a cohort study of 339 647 people in England. Thorax. 2024;79(3):202-8.
10. Celli B, Locantore N, Yates JC, Bakke P, Calverley PMA, Crim C, et al. Markers of disease activity in COPD: an 8-year mortality study in the ECLIPSE cohort. Eur Respir J. 2021;57(3).
11. Barnes PJ. Inflammatory endotypes in COPD. Allergy. 2019;74(7):1249-56.
12. Agustí A, Christenson S, Han M, Singh D. New Frontiers in Chronic Obstructive Pulmonary Disease: Where Are We Heading? EMJ Respiratory. 2022:2-10.
13. Singh D, Kolsum U, Brightling CE, Locantore N, Agusti A, Tal-Singer R, investigators E. Eosinophilic inflammation in COPD: prevalence and clinical characteristics. Eur Respir J. 2014;44(6):1697-700.
14. Casanova C, Celli BR, de-Torres JP, Martinez-Gonzalez C, Cosio BG, Pinto-Plata V, et al. Prevalence of persistent blood eosinophilia: relation to outcomes in patients with COPD. Eur Respir J. 2017;50(5).
15. Halpin DMG, de Jong HJI, Carter V, Skinner D, Price D. Distribution, Temporal Stability and Appropriateness of Therapy of Patients With COPD in the UK in Relation to GOLD 2019. EClinicalMedicine. 2019;14:32-41.
16. Oshagbemi OA, Burden AM, Braeken DCW, Henskens Y, Wouters EFM, Driessen JHM, et al. Stability of Blood Eosinophils in Patients with Chronic Obstructive Pulmonary Disease and in Control Subjects, and the Impact of Sex, Age, Smoking, and Baseline Counts. Am J Respir Crit Care Med. 2017;195(10):1402-4.
17. Oshagbemi OA, Franssen FME, van Kraaij S, Braeken DCW, Wouters EFM, Maitland-van der Zee AH, et al. Blood Eosinophil Counts, Withdrawal of Inhaled Corticosteroids and Risk of COPD Exacerbations and Mortality in the Clinical Practice Research Datalink (CPRD). Copd. 2019;16(2):152-9.
18. Ajithkumar CS. Peripheral blood eosinophilia in COPD: prevalence and clinical characteristics. Indian Journal of Basic and Applied Medical Research. 2018;7(2):223-8.

19. Office for Health Improvement and Disparities. Public health profiles - COPD: QOF prevalence (all ages) 2024 [
20. Sanofi. [Data on File]. Hospital episode statistics for COPD; fiscal year 2022-23. Mat-xu-2403964 (v1.0). 2024.
21. Office for National Statistics (ONS). Deaths registered in England and Wales. 2023 dataset.
22. Institute for Health Metrics and Evaluation. Health research by location: United Kingdom - England 2021 [Available from: https://www.healthdata.org/research-analysis/health-by-location/profiles/united-kingdom-england.
23. Office for Health Improvement and Disparities. INteractive Health Atlas of Lung conditions in England (INHALE): March 2023 update 2023 [Available from: https://www.gov.uk/government/statistics/interactive-health-atlas-of-lung-conditions-in-england-inhale-march-2023-update/interactive-health-atlas-of-lung-conditions-in-england-inhale-march-2023-update.
24. Public Health England. The 2nd Atlas of variation in risk factors and healthcare for respiratory disease in England. 2019 [Available from: https://fingertips.phe.org.uk/profile/atlas-of-variation.
25. Shavelle RM, Paculdo DR, Kush SJ, Mannino DM, Strauss DJ. Life expectancy and years of life lost in chronic obstructive pulmonary disease: findings from the NHANES III Follow-up Study. Int J Chron Obstruct Pulmon Dis. 2009;4:137-48.
26. Sanofi. [Data on File] COPD Patient Journey Research - August 2023. 2023.
27. Miravitlles M, Ribera A. Understanding the impact of symptoms on the burden of COPD. Respiratory research. 2017;18(1):67.
28. Ding B, Judge D, Small M, Bent-Ennakhil N, Siddiqui S. Functional performance in patients with COPD: association with treatment regimen, GOLD group, lung function, and symptom burden in a cross-sectional study. Int J Chron Obstruct Pulmon Dis. 2018;13:2785-96.
29. Yohannes AM, Kaplan A, Hanania NA. Anxiety and depression in chronic obstructive pulmonary disease: recognition and management. Journal of Family Practice. 2018;67(2):S11-S.
30. Maurer J, Rebbapragada V, Borson S, Goldstein R, Kunik ME, Yohannes AM, Hanania NA. Anxiety and depression in COPD: current understanding, unanswered questions, and research needs. Chest. 2008;134(4):43S-56S.
31. Marsh S, Guck TP. Anxiety and depression: easing the burden in COPD patients. J Fam Pract. 2016;65(4):246-56.
32. Blakemore A, Dickens C, Guthrie E, Bower P, Kontopantelis E, Afzal C, Coventry PA. Depression and anxiety predict health-related quality of life in chronic obstructive pulmonary disease: systematic review and meta-analysis. International journal of chronic obstructive pulmonary disease. 2014:501-12.
33. Miravitlles M, Molina J, Quintano JA, Campuzano A, Pérez J, Roncero C, Investigators DS. Factors associated with depression and severe depression in patients with COPD. Respiratory Medicine. 2014;108(11):1615-25.
34. Hong YJ, Kim Y, Moon J-Y, Park S, Lee J-K, Jung K-S, et al. Associations between depression and anxiety index and frequency of acute exacerbation in chronic obstructive pulmonary disease. Therapeutic Advances in Respiratory Disease. 2023;17:17534666231216591.
35. Gruenberger JB, Vietri J, Keininger DL, Mahler DA. Greater dyspnea is associated with lower health-related quality of life among European patients with COPD. Int J Chron Obstruct Pulmon Dis. 2017;12:937-44.
36. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1998;157(5 Pt 1):1418-22.

37. Foo J, Landis SH, Maskell J, Oh YM, van der Molen T, Han MK, et al. Continuing to Confront COPD International Patient Survey: Economic Impact of COPD in 12 Countries. PLoS One. 2016;11(4):e0152618.

38. Asthma + Lung UK. Delayed diagnosis and unequal care: The reality for people with chronic obstructive pulmonary disease (COPD) in the UK in 2022. 2022.

39. Gautun H, Werner A, Luras H. Care challenges for informal caregivers of chronically ill lung patients: results from a questionnaire survey. Scand J Public Health. 2012;40(1):18-24.

40. Miravitlles M, Peña-Longobardo LM, Oliva-Moreno J, Hidalgo-Vega Á. Caregivers' burden in patients with COPD. Int J Chron Obstruct Pulmon Dis. 2015;10:347-56.

41. Asthma + Lung UK. Investing in breath: Measuring the economic cost of asthma and COPD in the UK and identifying ways to reduce it through better diagnosis and care. 2023.

42. National Institute for Health and Care Excellence. Chronic obstructive pulmonary disease in over 16s: diagnosis and management. 2018;2024(February 7).

43. Asthma + Lung UK. How is COPD diagnosed? 2022.

44. Albert RK, Connett J, Bailey WC, Casaburi R, Cooper JA, Jr., Criner GJ, et al. Azithromycin for prevention of exacerbations of COPD. N Engl J Med. 2011;365(8):689-98.

45. BMJ. Chronic obstructive pulmonary disease (COPD) 2024 [Available from: https://bestpractice.bmj.com/topics/en-us/7/management-approach.

46. Martinez FJ, Calverley PM, Goehring UM, Brose M, Fabbri LM, Rabe KF. Effect of roflumilast on exacerbations in patients with severe chronic obstructive pulmonary disease uncontrolled by combination therapy (REACT): a multicentre randomised controlled trial. Lancet. 2015;385(9971):857-66.

47. Martinez FJ, Rabe KF, Sethi S, Pizzichini E, McIvor A, Anzueto A, et al. Effect of Roflumilast and Inhaled Corticosteroid/Long-Acting β2-Agonist on Chronic Obstructive Pulmonary Disease Exacerbations (RE(2)SPOND). A Randomized Clinical Trial. Am J Respir Crit Care Med. 2016;194(5):559-67.

48. Munoz-Esquerre M, Diez-Ferrer M, Monton C, Pomares X, Lopez-Sanchez M, Huertas D, et al. Roflumilast added to triple therapy in patients with severe COPD: a real life study. Pulm Pharmacol Ther. 2015;30:16-21.

49. Cilli A, Bal H, Gunen H. Efficacy and safety profile of roflumilast in a real-world experience. J Thorac Dis. 2019;11(4):1100-5.

50. Salvesen ONU, Davidsen JR, Pottegard A, Henriksen DP. Roflumilast Usage from 2010 to 2016: A Danish Nationwide Drug Utilization Study. Basic Clin Pharmacol Toxicol. 2018;123(3):314-9.

51. Garudadri S, Woodruff PG. Targeting Chronic Obstructive Pulmonary Disease Phenotypes, Endotypes, and Biomarkers. Ann Am Thorac Soc. 2018;15(Suppl 4):S234-S8.

52. Higham A, Beech A, Wolosianka S, Jackson N, Long G, Kolsum U, et al. Type 2 inflammation in eosinophilic chronic obstructive pulmonary disease. Allergy. 2021;76(6):1861-4.

53. Fieldes M, Bourguignon C, Assou S, Nasri A, Fort A, Vachier I, et al. Targeted therapy in eosinophilic chronic obstructive pulmonary disease. ERJ Open Res. 2021;7(2).

54. Bhatt SP, Rabe KF, Hanania NA, Vogelmeier CF, Cole J, Bafadhel M, et al. Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts. N Engl J Med. 2023;389(3):205-14.

55. Bhatt SP, Rabe KF, Hanania NA, Vogelmeier CF, Bafadhel M, Christenson SA, et al. Dupilumab for COPD with Blood Eosinophil Evidence of Type 2 Inflammation. N Engl J Med. 2024.

56. Day SJ, Altman DG. Blinding in clinical trials and other studies. BMJ. 2000;321(7259):504.

57. Sanofi. [Data on File] CSR: 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). 2023 December 14,.

58. Sanofi. [Data on File] Summary of Clinical Efficacy (Chronic Obstructive Pulmonary Disease). 2023 December 18.

59. EXACT-RS Initiative. E-RS (EXACT-Respiratory Symptoms) User Manual (Version 3.0). 2014.

60. Norddeutscher Rundfunk. COPD: Neues Medikament Dupilumab bei schweren Verläufen. Available at: https://www.ndr.de/fernsehen/sendungen/visite/COPD-Neues-Medikament-Dupilumab-bei-schweren-Verlaeufen,visite24060.html. 2024.

61. Sanofi. Dupixent approved in the US as the first-ever biologic medicine for patients with COPD 2024 [updated 27 September 2024. Available from: https://www.sanofi.com/en/media-room/press-releases/2024/2024-09-27-13-35-00-2954551.

62. Sanofi. [Data on File] Summary of Clinical Safety (Chronic Obstructive Pulmonary Disease). 2023 December 19.

63. Sanofi. [Data on File] Periodic benefit risk evaluation report. Dupilumab. Covered period: 29-Mar-2023 to 28-Mar-2024. 2024.

64. Atlantis E, Fahey P, Cochrane B, Smith S. Bidirectional associations between clinically relevant depression or anxiety and COPD: a systematic review and meta-analysis. Chest. 2013;144(3):766-77.

65. Punekar YS, Wurst K, Shukla A. Resource Use and Costs up to Two Years Post Diagnosis Among Newly Diagnosed COPD Patients in the UK Primary Care Setting: A Retrospective Cohort Study. COPD. 2015;12(3):267-75.

66. Merinopoulou E, Raluy-Callado M, Ramagopalan S, MacLachlan S, Khalid JM. COPD exacerbations by disease severity in England. Int J Chron Obstruct Pulmon Dis. 2016;11:697-709.

67. Fletcher MJ, Upton J, Taylor-Fishwick J, Buist SA, Jenkins C, Hutton J, et al. COPD uncovered: an international survey on the impact of chronic obstructive pulmonary disease [COPD] on a working age population. BMC Public Health. 2011;11:612.

68. World Health Organization. Model List of Essential Medicines. 23rd list. 2023 [updated 26 Jul. Available from: https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.02.

69. European Medicines Agency (EMA). Azithromycin-containing medicinal products for systemic use - referral 2024 [updated 15 May. Available from: https://www.ema.europa.eu/en/medicines/human/referrals/azithromycin-containing-medicinal-products-systemic-use.

70. UK Health Security Agency. Antibiotic resistant infections and associated deaths increase 2023 [Available from: https://www.gov.uk/government/news/antibiotic-resistant-infections-and-associated-deaths-increase.

71. Benhamou D, Weiss M, Borms M, Lucaci J, Girgis H, Frolet C, et al. Assessing the Clinical, Economic, and Health Resource Utilization Impacts of Prefilled Syringes Versus Conventional Medication Administration Methods: Results From a Systematic Literature Review. Ann Pharmacother. 2024;58(9):921-34.

72. Milpharm. Roflumilast Summary of Product Characteristics. 2024.

73. Ji Z, de Miguel-Díez J, Castro-Riera CR, Bellón-Cano JM, Gallo-González V, Girón-Matute WI, et al. Differences in the Outcome of Patients with COPD according to Body Mass Index. J Clin Med. 2020;9(3).

74. Office for National Statistics (ONS). Inequalities in mortality involving common physical health conditions, England: 21 March 2021 to 31 January 2023. 2023.

75. Office for Health Improvement and Disparities. Public health profiles by deprivation deciles 2024 [Available from: https://fingertips.phe.org.uk.

76. Martin A, Badrick E, Mathur R, Hull S. Effect of ethnicity on the prevalence, severity, and management of COPD in general practice. Br J Gen Pract. 2012;62(595):e76-81.

77. Francis A, Cumella A, editors. Unmet need and barriers in provision of pulmonary rehabilitation for people with COPD: findings from a large UK survey. ERS; 2023.

78. Sanofi. This World COPD Day, let's focus on closing the respiratory inequality gap, and #BreatheEqual 2023 [Available from: https://www.sanofi.co.uk/en/news/2023/world-copd-day.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Dupilumab for treating moderate to severe chronic obstructive pulmonary disease [ID6235]

Clarification questions

November 2024

File name	Version	Contains confidential information	Date
ID6235_Dupilumab EAG clarification questions_06122024_CIC	1	No	6th December 2024

Model update

During the clarification period we acted on the comments of the EAG to fix errors that they observed along with some additional errors we identified in the original model. These fixes have resulted in very little change to the original ICER (probabilistic: £25,793 vs. £25,520). A change log has been provided in Appendix 1. The updated set of results originally presented in the CS is provided in Appendix 2. The impact on the base case is shown below in Table 1 and Table 2.

Table 1. Original base case

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Probabilistic base case							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,793
Background Therapy	[redacted]	[redacted]	[redacted]				
Deterministic base case							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,668
Background Therapy	[redacted]	[redacted]	[redacted]				

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Table 2. Updated base case

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Probabilistic base case							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,624
Background Therapy	[redacted]	[redacted]	[redacted]				
Deterministic base case							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,515
Background Therapy	[redacted]	[redacted]	[redacted]				

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

All of the analyses presented in the following response to the clarification questions have been calculated using the updated model [ID6235_Markov CEM for dupilumab_UK_v5.0_Dec6]

Section A: Clarification on effectiveness data

Methods

A1. Priority question: The EAG notes that missing data for the continuous outcomes in BOREAS and NOTUS were imputed based on a missing at random assumption. For each relevant outcome in each trial, please can the company confirm how much data were imputed for:

a) **the dupilumab arm;**
b) **the placebo arm.**

In the Mixed Model for Repeated Measures (MMRM) applied to continuous endpoints, based on a missing at random assumption, missing data were not formally imputed since all observed data were taken into account.

The proportion of patients who completed at Week 52 for the St. George's Respiratory Questionnaire (SGRQ) and who assessed Forced Expiratory Volume in one second (FEV_1) at Week 52 are reported below for the pooled Intent-to-Treat (ITT) population of patients who had the opportunity to reach Week 52. (Table 3 and Table 4).

Table 3. Pooled ITT patients with an opportunity to reach W52 - SGRQ response rate (BOREAS and NOTUS)

Week 52	Placebo (N=830)	Dupilumab (N=830)	All (N=1660)
Number of patients remaining in the study	781	792	1573
Number of completed questionnaires (% in relation to ITT population)	724 (87.2)	745 (89.8)	1469 (88.5)
Number of completed questionnaires (% in relation to ITT population remaining in the study)	724 (92.7)	745 (94.1)	1469 (93.4)

ITT = intent to treat; SGRQ = St. George's Respiratory Questionnaire

Table 4. Pooled ITT patients with an opportunity to reach W52 – pre bronchodilator FEV_1 response rate (BOREAS and NOTUS)

Week 52	Placebo (N=830)	Dupilumab (N=830)	All (N=1660)
Number of patients remaining in the study	777	788	1565
Number of completed assessment (% in relation to ITT population)	744 (89.6)	759 (91.4)	1503 (90.5)
Number of completed assessment (% in relation to ITT population remaining in the study)	744 (95.8)	759 (96.3)	1503 (96.0)

ITT = intent to treat

A2. Priority question: Please provide a version of the results from the pooled analysis based on the observed data without imputation.

Although missing data were not formally imputed in the MMRM analyses, we have provided the results of the analyses of covariance (ANCOVA) at Week 52 for change from baseline at week 52 in FEV_1 and SGRQ, as shown in Table 5 and Table 6. The tables shows that the results for the two approaches are similar, with only minimal differences observed between them.

Table 5. Analysis of change from baseline in SGRQ total score at week 52 using MMRM and ANCOVA - Pooled ITT Population with an opportunity to reach Week 52. (BOREAS and NOTUS)

SGRQ total score	MMRM[a]		ANCOVA[b]	
Change from baseline at Week 52	**Placebo (N=936)**	**Dupilumab (N=938)**	**Placebo (N=830)**	**Dupilumab (N=830)**
LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
LS Mean Diff, 95% CI	[redacted]		[redacted]	
P-value vs. placebo	0.0001		0.0001	

[a]Based on a MMRM model with the change from baseline in SGRQ total score up to Week 52 as response variables, and treatment group, study (if pooled), region (pooled country), ICS dose, smoking status at screening, treatment-by-visit interaction, baseline SGRQ total score, and SGRQ baseline-by-visit interaction as covariates
[b]Based on a linear regression model (ANCOVA) on change from baseline at week 52 as the response variable and corresponding baseline value, treatment group, region (pooled country), ICS dose, smoking status at screening and study as covariates.

Table 6. Analysis of change from baseline in pre-bronchodilator FEV_1 (L) at week 52 (ANCOVA) - Pooled ITT Population. (BOREAS and NOTUS)

FEV_1	MMRM[a]		ANCOVA[b]	
Change from baseline at Week 52	**Placebo (N=936)**	**Dupilumab (N=938)**	**Placebo (N=830)**	**Dupilumab (N=830)**
LS Mean (SE), litres	[redacted]	[redacted]	[redacted]	[redacted]
LS Mean Diff, 95% CI, litres	[redacted]		[redacted]	
P-value vs. placebo	0.0001		0.0001	

[a]Based on a MMRM model with the change from baseline in pre-bronchodilator FEV_1 up to Week 52 as response variables, and treatment group, study (if pooled), age, sex, height, region (pooled country), ICS dose, smoking status at screening, visit, treatment-by-visit interaction, baseline pre-bronchodilator FEV_1, and FEV_1 baseline-by-visit interaction as covariates.
[b]Based on a linear regression model (ANCOVA) on change from baseline at week 52 as the response variable and corresponding baseline value, treatment group, age, sex, height, region (pooled country), ICS dose, smoking status at screening and study as covariates.

A3. Priority question: The company submission (Document B, page 74) states that clinically meaningful between-group differences were reached for all endpoints in the BOREAS trial, and for the primary analysis and first three secondary endpoints in the NOTUS trial.

a) **Please clarify what threshold was used to determine a clinically meaningful difference for each endpoint in the trials and in the pooled analysis.**

b) **Please provide references or justification for the choice of each threshold used.**

In the primary publication of BOREAS results, the authors concluded that the trial "showed consistency with respect to the clinically relevant results across multiple aspects of important COPD end points and subgroups". In the NOTUS publication, authors concluded that "A 34% relative reduction in moderate or severe exacerbations with dupilumab as compared with placebo observed in this trial is "clinically significant".

There is no validated decrease in COPD exacerbation rate considered an MCID. However, any statistically significant reduction in COPD exacerbations between dupilumab and placebo might be considered "clinically meaningful", given the serious clinical consequences associated with exacerbations, both moderate and severe. Additionally, the moderate or severe exacerbation rate reduction for dupilumab was approximately 63% versus baseline, and the proportion of patients who did not exacerbate at all was 64%. UK clinical expert opinion noted that other interventions that decrease exacerbation rate in the 20-25% range are often considered clinically significant, and a 22% exacerbation reduction can be anchored to an SGRQ MCID of 4 points.(1) Thus, the BOREAS and NOTUS exacerbation reduction rates are clinically meaningful, based on the informal clinically significant threshold above. (Note that dupilumab was added to current standard of care so these results represent benefits over and above inhaled therapies).

Any statistically significant improvement in FEV_1 might be considered clinically significant in the context of a disease characterised by progressive lung function decline. This decline is associated with an increased risk of mortality. An MCID for

FEV_1 improvement in COPD of 100 mL has been proposed but not widely accepted or validated.(2) We acknowledge that the mean improvement in pre-bronchodilator FEV_1 between dupilumab and placebo in the pooled analysis is close but less than 100 mL. However, 42.2% of dupilumab patients in the pooled analysis had a ≥100 mL FEV_1 improvement at week 12 versus baseline, versus 31.1% of placebo patients – an odds ratio versus placebo of 1.634 (1.350 to 1.977) p <.0001. Odds ratios for responders to treatment versus placebo in the 1.3-1.5 range may informally indicate “clinically meaningful”. Also, the mean improvement for dupilumab treated patients versus baseline was approximately 140 mL. Furthermore, for an improvement in FEV_1 to be “clinically meaningful” to the patient, its effect should be captured in quality of life measures, and for dupilumab versus placebo and dupilumab versus baseline, patients reported improved SGRQ. UK clinical expert opinion noted that a 100 mL or more improvement in FEV_1 would generally be considered clinically significant depending on the individual patient’s starting point – a lower FEV_1 improvement (e.g., 50 mL) might still be clinically significant for a patient who’s FEV_1 was already low (as was the case for many patients in the BOREAS and NOTUS studies).(3)

An MCID for SGRQ improvement of ≥ 4 points is widely accepted and validated.(4) We acknowledge that the mean improvement in SGRQ between dupilumab and placebo is close to 4 points, but point out that 51.4% of dupilumab patients in the pooled analysis had a ≥ 4 points improvement versus baseline, versus 44.6% of placebo patients - an odds ratio versus placebo of 1.311 (1.070 to 1.607) p =0.0089. Odds ratios for responders to treatment versus placebo in the 1.3-1.5 range may informally indicate “clinically meaningful”. Also, the mean improvement for dupilumab treated patients versus baseline was approximately 10 points. It is worth mentioning that the developers of the SGRQ recognized that the 4 point threshold is very high “for judging the efficacy of a treatment”(5) if we consider that “Whilst many treatment studies compare treatments by estimating the mean difference, there is a significant disadvantage to this approach, not least because there is a risk that if the mean difference is <4 units, the treatment may be judged to be ineffective. However, for the mean difference to exceed 4.0, more than half of patients would need to improve by ≥4 units (if the data are normally distributed)”, which was the case for the dupilumab treated patients in the pooled analysis. UK clinical expert opinion noted

that QoL improvement is desirable but hard to achieve with other medical interventions individually, such that 2-2.5 point between-group differences may be clinically relevant.(6) Overall it was felt that the improvement in SGRQ with dupilumab treatment versus placebo of 3.4 would be considered clinically meaningful.

There is no validated MCID for ER-S: COPD total score improvement in COPD. However, we have empirically derived an anchor-based 3.7 point improvement threshold to aid in the interpretation of clinical meaningfulness of mean changes for E-RS: COPD total score at the patient level, based on BOREAS data. In the pooled analysis, the mean change in E-RS: COPD total score between baseline and week 52, for patients treated with dupilumab, was approximately 2.5 points, and 27.3% of dupilumab patients had a ≥3.7 improvement, versus 21.6% of placebo patients - an odds ratio versus placebo of 1.386 (1.097 to 1.751) p =0.0063. Odds ratios for responders to treatment versus placebo in the 1.3-1.5 range may informally indicate “clinically meaningful”.

Overall, we recognise that the use of the term “clinically meaningful”, used to describe outcome benefits for dupilumab, is relatively subjective and difficult to formally measure. However, UK clinical expert opinion has validated the term being applied to some of the individual measures above. And, taken as a whole, they believe the results seen in the BOREAS and NOTUS studies do represent clinical meaningful benefits to patients treated with dupilumab. Lastly, we point out that the economic model applies a treatment efficacy assessment at 52 weeks to patients who exacerbate more frequently compared to their baseline; the responder population have higher magnitude benefits in other outcomes (such as FEV_1, SGRQ and E-RS: COPD), compared to the BOREAS and NOTUS ITT populations.

A4. Clinical experts advising the EAG noted that patients should be provided with the fundamentals of care (such as smoking cessation advice, vaccinations and pulmonary rehabilitation) prior to treatment initiation.

a) Please clarify if, and what, other treatments were provided to patients prior to, or during, the trials that are considered the fundamentals of COPD care.

b) Please comment on the likely impact on the treatment effect for people who received the fundamentals of care compared to those who did not.

In England, the 5 fundamentals of COPD care are: offering smoking cessation advice, vaccinations and pulmonary rehabilitation, a personalised self-management plan and optimisation of treatment and comorbidities. Ideally these are offered to patients throughout all stages of COPD, not just prior to particular treatments (such as dupilumab). All patients in the dupilumab clinical studies had a physician diagnosis of COPD for 1 year prior to inclusion and were expected to have received appropriate COPD care before and during this time. The nature of such care may have differed for study participants from different countries, but could reasonably be expected to be broadly similar to the 5 fundamentals. However, it should be noted that "offering" the fundamentals does not equate to fulfilling them, and that even only offering can be problematic to achieve consistently. In the Asthma & Lung UK '*Life with a Lung Condition Survey 2024'* which ran from January to March 2024 and received 12,700 responses across the UK only 9% of patients who answered (n = 4261) had received all 5 fundamentals. The proportion of patients receiving 0 to 5 of the elements is shown in Table 7 below.

Table 7. Number of elements of fundamentals of COPD care

Number of elements	Proportion receiving the elements	Number of patients
0	14%	601
1	27%	1141
2	30%	1280
3	19%	792
4	1%	47
5	9%	400
Total	100%	4261

We do, however, agree with the principle that all patients should ideally be offered each of the eligible 5 fundamentals, prior to and beyond treatment with an advanced medicine (such as dupilumab). But also point out that patients recruited into the BOREAS and NOTUS studies were uncontrolled (experiencing exacerbations), symptomatic, and with poor lung function, despite standard of care up to this point.

Considering the general expectation of standard of care in different countries, the 5 fundamentals were not specific inclusion criteria for patients entering the dupilumab studies. Specific additionally information for smoking cessation, pulmonary rehabilitation and vaccination are provided below.

Smoking status was recorded at baseline, but not whether smoking cessation advice had been offered, fulfilled or successfully completed, either prior to study initiation or during study conduct. Therefore, given available data from the BOREAS and NOTUS studies, we provide an investigation of treatment effect only for patients who were former or current smokers at baseline. Such a treatment effect would not reflect the offering of smoking cessation advice per se, but may reflect the proportion which are fulfilled and successfully completed (stopped smoking). Dupilumab versus placebo exacerbation reduction and FEV_1 improvement outcomes for current smokers vs former smokers was already provided in the CS and is reproduced below in Figure 1 and Figure 2.

Figure 1. Forest plot of relative risk on the annualised rate of moderate or severe COPD exacerbations during the 52-week treatment period by smoking status - Pooled ITT population.

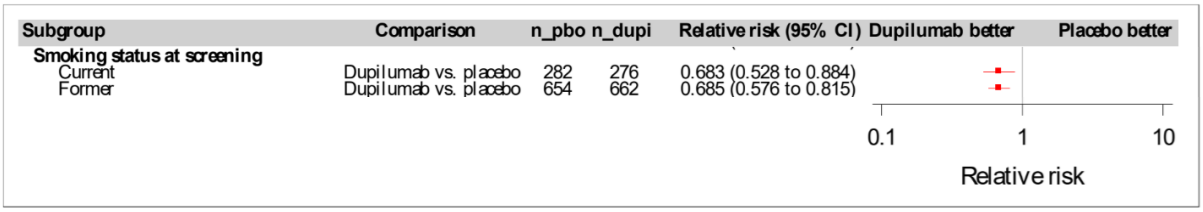
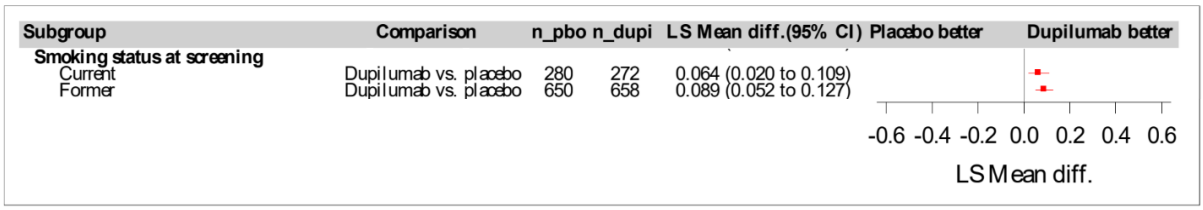


Figure 2. Forest plot of LS mean difference in the change from baseline in pre-bronchodilator FEV_1 at Week 12 by disease characteristics subgroups - Pooled ITT population



Exacerbation reduction for the both the former smoker and current smoker cohorts were statistically significant at ~32%. LS mean difference in FEV_1 vs. placebo was statistically significant in both groups (Current smoker: 64 mL. Former smoker: 89 mL).

Patients who had started pulmonary rehabilitation (PR) <4 weeks prior to screening were excluded from study participation (but those in in the maintenance phase of a rehabilitation program could be included). However, prior or during study pulmonary rehabilitation was not recorded. We therefore cannot provide any comparison of outcomes for patients who had completed pulmonary rehabilitation versus those who had not. UK clinical opinion highlighted that PR provision in the real world is not comprehensive to those eligible, and also subject to regional inequality, and that attendance and completion of PR can be difficult for a proportion of patients where the PR clinic is distant and for those with higher burden/risk, and certainly unlikely to be delivered on an annual basis (PR benefits are generally limited to12 months) – PR is a fundamental of care that has proven difficult to appropriately and comprehensively provide, and therefore cannot be considered current standard of care. UK clinical experts are also concerned that delivery of the 5 fundamentals (including PR) may create a restrictive “funnel”, through which patients “have to pass” to become eligible for advanced treatments. In this scenario, it is likely that patients with a higher burden of disease would be disproportionately excluded from some treatments – discriminating against those with the most need, and widening inequality gaps. Additionally, for those patients who do begin a PR programme, an acute exacerbation will often prematurely terminate completion – PR is easier to deliver for those with stable COPD, and we point out that dupilumab treatment is for patients who frequently exacerbate. For patients who might be able to complete a PR programme in the 12 months before dupilumab treatment, clinical expert opinion suggested that QoL benefits of both treatments would be at least additive, since they act through very different mechanisms - PR acts on muscle/strength/exercise capacity whereas dupilumab inhibits underlying inflammation. They suggest that no treatment modifying effect for dupilumab lung function benefits would be expected.

Some information was captured in the BOREAS and NOTUS studies regarding patient vaccinations in the 6 months prior to screening, and also as concomitant

medication during the treatment period, including that for various COVID, flu and pneumococcal vaccines. However, this was not a systemic capture of data (similarly to other phase 3 COPD studies) and is likely to be quantitively incomplete, and we therefore don't believe an analysis of these patients would be informative. UK clinical expert opinion highlighted that COVID, flu and pneumococcal vaccination should reduce the rate of these exacerbation triggers for patients, and therefore provide a benefit in exacerbation reduction. However, vaccination works more effectively at population level, and vaccinated individuals may not be completely protected (eg pneumococcal vaccination may help prevent pneumonia, but not necessarily pneumococcal infection). There are also other common infective exacerbation triggers not addressed by vaccination (eg rhinovirus, RSV). Moreover, vaccination and dupilumab reduce exacerbations through entirely different mechanisms, and therefore UK clinical experts believe that prior vaccination would not be a treatment modifier for dupilumab (benefits may be additive).

COVID-19

A5. The company submission reports that, due to COVID-19, some on-site visits and assessments were replaced with remote monitoring or telephone visits.

a) provide information on the proportion of visits that were replaced with remote monitoring or telephone calls;

Following protocol amendments telephone visits were included as an option in both BOREAS and NOTUS. The rationale for the protocol amendment was to decrease the burden of onsite visits for patients while maintaining patient safety and data quality; to minimise COVID-19 pandemic-related risks in vulnerable and elderly population of COPD patients.

Table 8 below describes the proportion of visits impacted by Covid-19 in the pooled ITT population, broken down by the type of impact (complete visit done but delayed, missing data visit partially done by phone, missing data visit partially done on site). The total number of impacted visits was low at 2.5% (392/16055) across 936 placebo patients and 2.1% (347/16238) across 938 dupilumab patients. The proportion of visits delayed remained low (<1%) throughout the study; the proportion

of visits partially done by phone ranged from 0.1 to 1.7%, and partially done on site was below 2.4%.

Table 8. Description of visits impacted by Covid-19 - Pooled ITT population

Visit as per eCRF	Placebo	Dupilumab 300 mg q2w	All
	(N=936)	(N=938)	(N=1,874)
VISIT 1 SCREENING			
Number	936	938	1,874
Missing data visit partially done on site (due to COVID-19)	1 (0.1)	0	1 (<0.1)
Regular visit	935 (99.9)	938 (100)	1873 (>99.9)
VISIT 2 BASELINE WEEK 0			
Number	936	938	1,874
Regular visit	936 (100)	938 (100)	1874 (100)
VISIT 3 WEEK 2			
Number	918	925	1,843
Complete visit done but delayed (due to COVID-19)	0	1 (0.1)	1 (<0.1)
Missing data visit partially done by phone (due to COVID-19)	6 (0.7)	1 (0.1)	7 (0.4)
Missing data visit partially done on site (due to COVID-19)	1 (0.1)	3 (0.3)	4 (0.2)
Regular visit	911 (99.2)	920 (99.5)	1831 (99.3)
VISIT 4 WEEK 4			
Number	919	924	1,843
Complete visit done but delayed (due to COVID-19)	1 (0.1)	1 (0.1)	2 (0.1)
Missing data visit partially done by phone (due to COVID-19)	1 (0.1)	1 (0.1)	2 (0.1)
Missing data visit partially done on site (due to COVID-19)	6 (0.7)	4 (0.4)	10 (0.5)
Regular visit	911 (99.1)	918 (99.4)	1829 (99.2)
VISIT 5 WEEK 8			
Number	909	918	1,827
Complete visit done but delayed (due to COVID-19)	3 (0.3)	5 (0.5)	8 (0.4)
Missing data visit partially done by phone (due to COVID-19)	6 (0.7)	5 (0.5)	11 (0.6)
Missing data visit partially done on site (due to COVID-19)	11 (1.2)	14 (1.5)	25 (1.4)
Regular visit	889 (97.8)	894 (97.4)	1783 (97.6)
VISIT 6 WEEK 12			
Number	906	914	1,820
Complete visit done but delayed (due to COVID-19)	2 (0.2)	0	2 (0.1)
Missing data visit partially done by phone (due to COVID-19)	11 (1.2)	5 (0.5)	16 (0.9)
Missing data visit partially done on site (due to COVID-19)	17 (1.9)	16 (1.8)	33 (1.8)
Regular visit	876 (96.7)	893 (97.7)	1769 (97.2)
VISIT 7 WEEK 16			
Number	900	914	1,814

Visit as per eCRF	Placebo	Dupilumab 300 mg q2w	All
Complete visit done but delayed (due to COVID-19)	1 (0.1)	1 (0.1)	2 (0.1)
Missing data visit partially done by phone (due to COVID-19)	10 (1.1)	8 (0.9)	18 (1.0)
Missing data visit partially done on site (due to COVID-19)	18 (2.0)	15 (1.6)	33 (1.8)
Regular visit	871 (96.8)	890 (97.4)	1761 (97.1)
VISIT 8 WEEK 20			
Number	892	901	1,793
Complete visit done but delayed (due to COVID-19)	2 (0.2)	3 (0.3)	5 (0.3)
Missing data visit partially done by phone (due to COVID-19)	12 (1.3)	9 (1.0)	21 (1.2)
Missing data visit partially done on site (due to COVID-19)	26 (2.9)	12 (1.3)	38 (2.1)
Regular visit	852 (95.5)	877 (97.3)	1729 (96.4)
VISIT 9 WEEK 24			
Number	869	884	1,753
Complete visit done but delayed (due to COVID-19)	1 (0.1)	3 (0.3)	4 (0.2)
Missing data visit partially done by phone (due to COVID-19)	14 (1.6)	6 (0.7)	20 (1.1)
Missing data visit partially done on site (due to COVID-19)	24 (2.8)	18 (2.0)	42 (2.4)
Regular visit	830 (95.5)	857 (96.9)	1687 (96.2)
VISIT 10 WEEK 28			
Number	859	869	1,728
Complete visit done but delayed (due to COVID-19)	0	2 (0.2)	2 (0.1)
Missing data visit partially done by phone (due to COVID-19)	21 (2.4)	9 (1.0)	30 (1.7)
Missing data visit partially done on site (due to COVID-19)	19 (2.2)	14 (1.6)	33 (1.9)
Regular visit	819 (95.3)	844 (97.1)	1663 (96.2)
VISIT 11 WEEK 32			
Number	850	848	1,698
Complete visit done but delayed (due to COVID-19)	2 (0.2)	1 (0.1)	3 (0.2)
Missing data visit partially done by phone (due to COVID-19)	18 (2.1)	6 (0.7)	24 (1.4)
Missing data visit partially done on site (due to COVID-19)	3 (0.4)	5 (0.6)	8 (0.5)
Regular visit	827 (97.3)	836 (98.6)	1663 (97.9)
VISIT 12 WEEK 36			
Number	828	837	1,665
Complete visit done but delayed (due to COVID-19)	2 (0.2)	2 (0.2)	4 (0.2)
Missing data visit partially done by phone (due to COVID-19)	10 (1.2)	14 (1.7)	24 (1.4)
Missing data visit partially done on site (due to COVID-19)	19 (2.3)	19 (2.3)	38 (2.3)
Regular visit	797 (96.3)	802 (95.8)	1599 (96.0)
VISIT 13 WEEK 40			
Number	819	828	1,647

Visit as per eCRF	Placebo	Dupilumab 300 mg q2w	All
Missing data visit partially done by phone (due to COVID-19)	11 (1.3)	12 (1.4)	23 (1.4)
Missing data visit partially done on site (due to COVID-19)	3 (0.4)	4 (0.5)	7 (0.4)
Regular visit	805 (98.3)	812 (98.1)	1617 (98.2)
VISIT 14 WEEK 44			
Number	805	810	1,615
Complete visit done but delayed (due to COVID-19)	5 (0.6)	1 (0.1)	6 (0.4)
Missing data visit partially done by phone (due to COVID-19)	8 (1.0)	10 (1.2)	18 (1.1)
Missing data visit partially done on site (due to COVID-19)	20 (2.5)	12 (1.5)	32 (2.0)
Regular visit	772 (95.9)	787 (97.2)	1559 (96.5)
VISIT 15 WEEK 48			
Number	785	798	1,583
Complete visit done but delayed (due to COVID-19)	1 (0.1)	2 (0.3)	3 (0.2)
Missing data visit partially done by phone (due to COVID-19)	7 (0.9)	10 (1.3)	17 (1.1)
Missing data visit partially done on site (due to COVID-19)	6 (0.8)	6 (0.8)	12 (0.8)
Regular visit	771 (98.2)	780 (97.7)	1551 (98.0)
VISIT 16 (EOT)			
Number	766	782	1,548
Complete visit done but delayed (due to COVID-19)	5 (0.7)	3 (0.4)	8 (0.5)
Missing data visit partially done by phone (due to COVID-19)	7 (0.9)	9 (1.2)	16 (1.0)
Missing data visit partially done on site (due to COVID-19)	10 (1.3)	10 (1.3)	20 (1.3)
Regular visit	744 (97.1)	760 (97.2)	1504 (97.2)
VISIT 17 WEEK 56			
Number	745	759	1,504
Complete visit done but delayed (due to COVID-19)	0	1 (0.1)	1 (<0.1)
Missing data visit partially done by phone (due to COVID-19)	5 (0.7)	5 (0.7)	10 (0.7)
Missing data visit partially done on site (due to COVID-19)	7 (0.9)	11 (1.4)	18 (1.2)
Regular visit	733 (98.4)	742 (97.8)	1475 (98.1)
VISIT 18 WEEK 60			
Number	715	733	1,448
Complete visit done but delayed (due to COVID-19)	0	3 (0.4)	3 (0.2)
Missing data visit partially done by phone (due to COVID-19)	5 (0.7)	8 (1.1)	13 (0.9)
Missing data visit partially done on site (due to COVID-19)	6 (0.8)	14 (1.9)	20 (1.4)
Regular visit	704 (98.5)	708 (96.6)	1412 (97.5)
VISIT 19 (EOS)			
Number	698	718	1,416
Complete visit done but delayed (due to COVID-19)	3 (0.4)	6 (0.8)	9 (0.6)

Visit as per eCRF	Placebo	Dupilumab 300 mg q2w	All
Missing data visit partially done by phone (due to COVID-19)	8 (1.1)	7 (1.0)	15 (1.1)
Missing data visit partially done on site (due to COVID-19)	7 (1.0)	10 (1.4)	17 (1.2)
Regular visit	680 (97.4)	695 (96.8)	1375 (97.1)

b) Please provide further information on how telephone assessments and remote visits were conducted, including the measures taken to ensure that outcomes such as FEV_1 were recorded accurately.

As can be seen in Figure 3 telephone visits were made available for visits 7, 8, 10, 11, 13, 15, 17 and 18. These visits did not correspond to spirometry testing, and were used to review smoking status, prior and concomitant medications, at home Investigational Medicinal Product administration, data from the electronic diary, at home urine pregnancy test and adverse event reporting. COPD exacerbations and health care resource utilisation were reported by Investigators, so were not impacted by telephone visits. Given the low utilisation of telephone visits and the nature of the information collected during these visits it is unlikely that information recording and accuracy would have been compromised.

Figure 3 below shows the schedule of events for the recording of Spirometry taken from the Amended Clinical Trial Protocol 03 to EFC15805 (NOTUS) dated 29th August 2023. This is consistent with the amended trial protocol to BOREAS.

Figure 3. Spirometry schedule of events

	Screening	Randomization/ Baseline																												
VISIT	1	2[a,b]	3	4		5		6		7[s]		8[s]		9		10[s]		11[s]		12		13[s]		14		15[s]		16[c]	17[s]	18[s]	19
WEEK[a]	W-4 to W0	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52 (EOT)	56	60	64 (EOS)
Spirometry (pre-BD)[m,n]	X	X	X	X		X		X						X						X				X				X			X
Spirometry (post-BD)[m,n]	X	X	X	X		X		X						X						X								X			X

[a] Randomisation/baseline Visit is defined as Day 1. The visit schedule should be adhered to within ±1 week for the 4-week screening period, ±3 days for the randomised IMP treatment period and ±5 days for the post IMP treatment period. If more than 12 weeks since last on-site scheduled visit, then unscheduled visit is required within 3 weeks of missed scheduled visit (eg, if missed scheduled visit at Week 24, then unscheduled visit must be performed by week 27; If missed scheduled visit at week 36, then unscheduled must be performed by week 39). All the assessments of the missed scheduled on-site visit will need to be carried out at the unscheduled visit.
b All assessments at Visit 2 (Day 1) are to be conducted pre-IMP dose with the exception of the assessment of local tolerability of SC injections.
c End-of-treatment visit
m Spirometry will be done locally according to European Respiratory Society (ERS)/American Thoracic Society (ATS) 2005 guidance but measured by a central laboratory. Spirometry will be performed during a trough period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of

ipratropium for at least 8 hours, withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the measurements. Note: When both pre- and post-bronchodilator spirometry is assessed, the post-bronchodilator spirometry should be performed consistent with the mechanism of action of reliever (ie, 30 minutes for albuterol or other SABA).
n Following randomisation and during the treatment period - if spirometry is not performed at the scheduled visit it should be performed at the following on-site visit for all visits prior to Week 12. If not performed at Week 12 or at subsequent scheduled on-site visits, an unscheduled assessment is required within 3 weeks of the missed scheduled.
s Telephone visit

We note that a small proportion of visits in which spirometry was scheduled in Figure 3 (e.g., visit 6, week 12), were conducted by telephone (Table 8). Clearly spirometry could not be collected remotely. We recognise two possibilities in this circumstance; 1. for these time points, the telephone visits resulting in some missing spirometry data; or 2. Spirometry was appropriately recorded subsequently at the next on-site visit, according to protocol conditions. We have provided the data in Table 8 to address the reality of these possibilities, indicating that very little data was missed. Overall, we see no rationale to suggest that COVID and the consequent introduction of telephone visits in the protocols have had any meaningful impact on the quality or quantity of trial data captured, including data for FEV_1 and other spirometry measurements. A summary of missing data, and analyses using imputation and without, have been provided in response to EAG question A2.

A6. Priority question: The EAG notes that, in the pooled analysis, 9.0% of patients in the dupilumab group and 8.8% of patients in the placebo group experienced TEAEs associated with COVID-19, including COVID-19, COVID-19 pneumonia, suspected COVID-19 and a SARS-CoV-2 positive test (Document B, page 95). Please provide a subgroup analysis for each outcome in the pooled analysis, stratified by:

a) patients who experienced a TEAE associated with COVID-19; and

b) patients who did not report having a TEAE associated with COVID-19.

Outcomes stratified by TEAE associated with or without COVID are presented in Table 9, Table 10 and Table 11 below.

Table 9. TEAE associated with COVID-19 subgroup - Annualised rate of moderate or severe COPD exacerbations - Pooled ITT population with an opportunity to reach Week 52

Patients who experienced a TEAE associated with COVID-19 during the 52-week treatment period	Yes (N=166)		No (N=1708)	
	Placebo (N=82)	Dupilumab (N=84)	Placebo (N=854)	Dupilumab (N=854)
Number of participants with >=1 moderate or severe exacerbation event				
Number	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]
Number of moderate or severe exacerbation events - Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Total number of moderate or severe exacerbation events	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted annualised moderate or severe exacerbation event rate[a]				
Estimate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Relative risk vs. placebo (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]	[redacted]
Risk difference vs. placebo (95% CI)[b]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Derived using negative binomial model with the total number of the events occurring during the 52-week treatment period as the response variable, and treatment group, region (pooled country), ICS dose, baseline disease severity, study and number of moderate or severe COPD exacerbation events within one year prior to the study as covariates, and log-transformed treatment duration as an offset variable.
[b] Derived using delta method.

Table 10. TEAE associated with COVID-19 subgroup - SGRQ total score - Pooled ITT population with an opportunity to reach Week 52

Patients who experienced a TEAE associated with COVID-19 during the 52-week treatment period - SGRQ total score	Yes (N=164)		No (N=1496)	
	Placebo (N=82)	Dupilumab (N=82)	Placebo (N=748)	Dupilumab (N=748)
Baseline				
Number	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 52 - Change from baseline				
Number	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
LS Mean (SE)[a]	[redacted]	[redacted]	[redacted]	[redacted]
LS Mean Diff vs. placebo (95% CI)[a]		[redacted]		[redacted]
P-value vs. placebo		[redacted]		[redacted]

[a] Derived from MMRM model with change from baseline up to week 52 as the response variable and corresponding baseline value, treatment group, region (pooled country), ICS dose, smoking status at screening, study, visit, baseline-by-visit interaction and treatment-by-visit interaction as covariates.

Table 11. TEAE associated with COVID-19 subgroup - Pre - bronchodilator FEV_1 - Pooled ITT population with an opportunity to reach Week 52.

Patients who experienced a TEAE associated with COVID-19 with an opportunity to reach Week 52 - Pre-bronchodilator FEV_1(L)	Yes (N=164)		No (N=1496)	
	Placebo (N=82)	Dupilumab (N=82)	Placebo (N=748)	Dupilumab (N=748)
Baseline				
Number	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 52 - Change from baseline				
Number	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
LS Mean (SE)[a]	[redacted]	[redacted]	[redacted]	[redacted]
LS Mean Diff vs. placebo (95% CI)[a]	[redacted]	[redacted]	[redacted]	[redacted]
P-value vs. placebo	[redacted]	[redacted]	[redacted]	[redacted]

[a] Derived from MMRM model with change from baseline up to week 52 as the response variable and corresponding baseline value, treatment group, age, sex, height, region (pooled country), ICS dose, smoking status at screening, study, visit, baseline-by-visit interaction and treatment-by-visit interaction as covariates.

Results

A7. Priority question: The EAG notes that BOREAS and NOTUS included a 12-week post-treatment period (weeks 52 - 64) where dupilumab was withdrawn. Please provide the results of the pooled analysis for the 52 - 64 week period, for:

a) **People in the dupilumab arm who showed a response to treatment;**
b) **People in the dupilumab arm who did not show a response to treatment;**
c) **People in the placebo group.**

Clinicians consulted by us at an advisory board suggested a simple efficacy response criterion should be chosen to reflect maintenance of stable disease. Therefore, the rule chosen in the model is designed to reflect the fact that COPD is a progressive disease characterised by decline in lung function and exacerbations which are predictive of further exacerbations in the future. Stabilisation of disease is a good outcome for these patients with Type 2 inflammation who continue to exacerbate whilst on maximal inhaled therapy. The efficacy response criterion used in the model reflects this. In the tables that follow the definitions applied for the purposes of the biostatistical analyses are strictly:

- Responder

- *Improver* if the annualised rate of on-treatment severe exacerbations is strictly lower than the number of severe exacerbations prior to the study; if both numbers are equal and the annualised rate of on-treatment moderate exacerbation is strictly lower than the number of moderate exacerbations prior to the study.
- *Stable* if the annualised rate of on-treatment severe exacerbation is equal to the number of severe exacerbations prior to the study AND if the annualised rate of on-treatment moderate exacerbation is equal to the number of moderate exacerbations prior to the study.

- Non-responder
  - *Worsener* if the annualised rate of on-treatment severe exacerbations is strictly higher than the number of severe exacerbations prior to the study; if both numbers are equal and the annualised rate of on-treatment moderate exacerbations is strictly higher than the number of moderate exacerbations prior to the study.

The results from the BOREAS study for the annualised rate of exacerbations for the 12-week follow on period, lung function and SGRQ are provided below in Table 12 and Table 13. (Note the final follow up data for NOTUS are not available yet).

Table 12. Analysis of annualised rate of moderate or severe COPD exacerbations during the post-intervention follow-up period according to response during on-treatment period – BOREAS ITT population who completed the Week 52 study period

During the post-intervention follow-up period	Placebo	Dupilumab Responder	Dupilumab non-responder
	(N=440)	(N=426)	(N=19)
Number of participants with >=1 moderate or severe exacerbation event			
Number	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]
Number of moderate or severe exacerbation events			
Number	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]

During the post-intervention follow-up period	Placebo	Dupilumab Responder	Dupilumab non-responder
	(N=440)	(N=426)	(N=19)
≥4	[redacted]	[redacted]	[redacted]
Total number of moderate or severe exacerbation events	[redacted]	[redacted]	[redacted]
Total patient-years followed	[redacted]	[redacted]	[redacted]
Unadjusted annualised moderate or severe exacerbation event rate	[redacted]	[redacted]	[redacted]

Table 13. Summary of pre-bronchodilator FEV_1 (L) from Week 52 to Week 64 according to response during on-treatment period – BOREAS ITT population

During the post-intervention follow-up period	Placebo	Dupilumab Responder	Dupilumab non-responder
	(N=471)	(N=443)	(N=24)
Week 52			
Number	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]	[redacted]
Number	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]
Week 64			
Number	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]	[redacted]
Number	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]

Table 14. Summary of SGRQ total score from Week 52 to Week 64 according to response during on-treatment period – BOREAS ITT population

During the post-intervention follow-up period	Placebo	Dupilumab Responder	Dupilumab non-responder
	(N=461)	(N=437)	(N=24)
Week 52			
Number	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]

During the post-intervention follow-up period	Placebo	Dupilumab Responder	Dupilumab non-responder
	(N=461)	(N=437)	(N=24)
Median	[redacted]	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]
Change from baseline			
Number	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]	[redacted]
Min ; Max	[redacted]	[redacted]	[redacted]
Week 64			
Number	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]
Change from baseline			
Number	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]

Table 15. Proportion of participants with SGRQ improvement >= 4 points (Responder) at Week 52 and Week 64 according to response during on-treatment period – BOREAS ITT population

During the post-intervention follow-up period	Placebo	Dupilumab Responder	Dupilumab Non-responder
	(N=471)	(N=444)	(N=24)
Week 52			
Number	[redacted]	[redacted]	[redacted]
SGRQ improvement ≥ 4 points	[redacted]	[redacted]	[redacted]
No SGRQ improvement ≥ 4 points	[redacted]	[redacted]	[redacted]
Week 64			
Number	[redacted]	[redacted]	[redacted]
SGRQ improvement ≥ 4 points	[redacted]	[redacted]	[redacted]
No SGRQ improvement ≥ 4 points	[redacted]	[redacted]	[redacted]

Two points should be considered when reviewing these results. First, a very low proportion of patients in the dupilumab group met the criteria for non-response (~5%) and secondly dupilumab was withdrawn from all patients at week 52. The half-life of dupilumab is approximately 17 to 20 days and the median time to non-detectable concentrations is 10 to 11 weeks (for 300 mg every 2 weeks).(7) Therefore, it is not

surprising that there is a drop off in efficacy across dupilumab responders and non-responders following dupilumab withdrawal across the 12 week follow up period.

A8. Priority question: Please provide the results from the pooled analysis of the annualised rate of moderate exacerbations (as provided for severe exacerbations in Table 27 of Document B).

The annualised rate of moderate exacerbations for the pooled ITT population is provided in Table 16 below.

Table 16. Pooled analysis annualised rate of moderate COPD exacerbations over the 52-week treatment period (pooled ITT population)

	Dupilumab (n=938)	Placebo (n=936)
Participants with ≥1 moderate exacerbations, n (%)	[redacted]	[redacted]
Adjusted annualised moderate exacerbation event rate		
Estimate (95% CI)	[redacted]	[redacted]
Rate ratio vs. placebo (95% CI); p-value	[redacted]	

A9. Please provide the results from the pooled analysis of the time to first moderate COPD exacerbation (as provided for time to first severe COPD exacerbation on page 82, Document B).

The Kaplan-Meier plot for time to first moderate exacerbation is provided in Figure 4 and the Time to first moderate COPD exacerbation event during the 52-week treatment period is presented in Table 17.

Figure 4. Kaplan-Meier plot of time to first moderate COPD exacerbation event during the 52-week treatment period

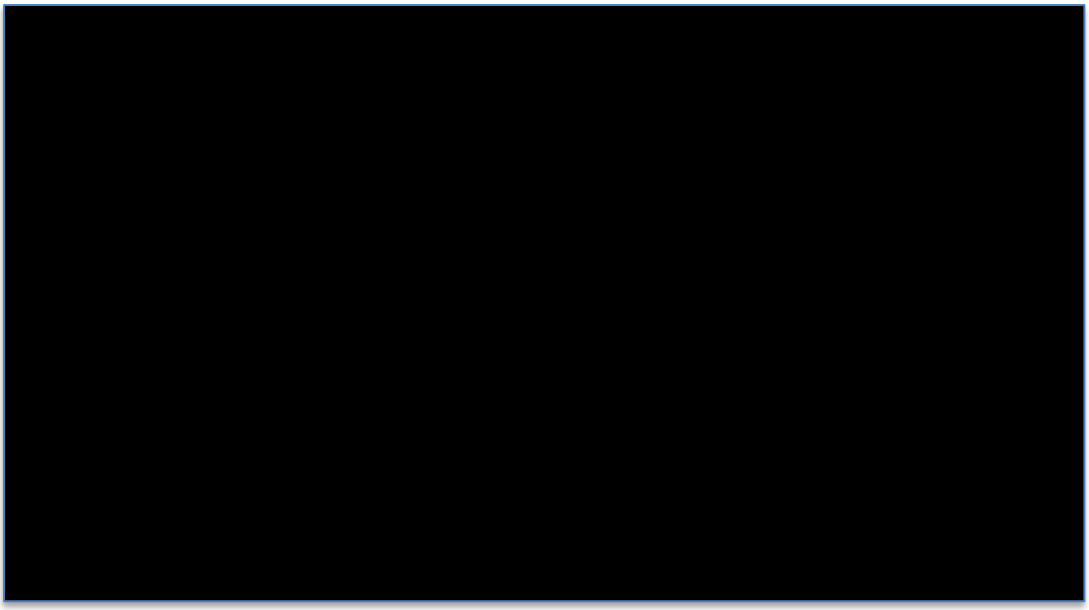


Table 17. Time to first moderate COPD exacerbation event during the 52-week treatment period

	Placebo	Dupilumab 300 mg q2w
	(N=936)	(N=938)
Number of participants with moderate exacerbation	[redacted]	[redacted]
Number of participants censored	[redacted]	[redacted]
Kaplan-Meier estimates for probability of a participant with >=1 event (95% CI) up to		
12 weeks	[redacted]	[redacted]
24 weeks	[redacted]	[redacted]
36 weeks	[redacted]	[redacted]
52 weeks	[redacted]	[redacted]
Hazard ratio[a]		[redacted]
P-value vs placebo[a]		[redacted]

Note: The time-to-event variable is defined as (date of the first event - randomisation date +1). For participants who have no event on or before Visit 16 or last contact date or database lock cut-off date, the time will be censored at the date of visit at Visit 16 or the last contact date or database lock cut-off date, whichever happens earlier.

[a] Derived using Cox regression model including the time to the first event as the dependent variable, and treatment groups, study, region (pooled country), ICS dose, smoking status at screening and baseline disease severity as covariates.

A10. Priority question: Please provide the overall mortality rate during the trial period for the dupilumab arm and the placebo arm from the pooled analysis.

A total of 37 deaths were reported in the pooled safety population: 34 were due to TEAEs with fatal outcome and 3 were post treatment AEs with fatal outcome. Of the 37 deaths 29 occurred during the treatment period and 8 occurred during the post - treatment period (including 5 deaths due to TEAEs and 3 deaths due to post

treatment AEs). Overall reported TEAEs with fatal outcome was generally consistent with what is anticipated in a population of patients with uncontrolled COPD.

Table 18. Mortality rate from the pooled analysis of BOREAS and NOTUS– Pooled safety population

n(%)	Placebo (N=934)	Dupilumab (N=938)
Death on study[a]	[redacted]	[redacted]
Death occurred during the TEAE period[b]	[redacted]	[redacted]
Death occurred during post-treatment period[c]	[redacted]	[redacted]
TEAE leading to death in the post-treatment period	[redacted]	[redacted]
Post-treatment AE leading to death in the post-treatment period	[redacted]	[redacted]

[a] Includes all deaths that occurred after the start of treatment up to the end of study (defined as last protocol planned visit or the resolution/stabilisation of all treatment emergent SAE and adverse events of pre-specified monitoring).
[b] Includes all deaths that occurred after the start of treatment up to last IMP date +98 days.
[c] Includes all deaths that occurred after the last IMP data +98 days.

A11. Priority question: The additional analyses section (Document B, page 83) states that, "Dupilumab led to a 30% reduction in the annualised total number of systemic corticosteroid courses compared to placebo".

a) Please clarify whether the 30% reduction refers to an overall reduction in systemic corticosteroid courses over the trial period, or whether this reflects a reduction in the number of systemic corticosteroid courses required per exacerbation.

The text in Section B.2.6.3.1; Additional analyses; page 83 states: "*Dupilumab led to a 30% reduction in the annualised total number of systemic corticosteroid courses compared to placebo".* We confirm that this refers to an overall reduction in systemic corticosteroid courses over the trial period.

b) If the 30% reduction refers to an overall reduction in systemic corticosteroid courses over the trial period, please provide information

on the number of systemic corticosteroid courses required per exacerbation in the dupilumab and placebo arms, for the:

i) BOREAS trial;

ii) NOTUS trial;

iii) pooled analysis.

The description of the number of SCS courses per exacerbation, calculated for each patient, is presented below in Table 19. The median number of courses per exacerbation was 1.0 but the mean number was slightly higher, reflecting a small number of exacerbations that received multiple courses of systemic corticosteroids.

Table 19. Individual total SCS courses per exacerbation in participants with SCS intake (taking into account adjudicated moderate exacerbations with SCS only)

	BOREAS (N=307)		NOTUS (N=251)		Pooled studies (N=558)	
	Placebo	Dupilumab	Placebo	Dupilumab	Placebo	Dupilumab
	(N=169)	(N=138)	(N=139)	(N=112)	(N=308)	(N=250)
Number	169	138	139	112	308	250
Mean (SD)	1.17 (0.54)	1.12 (0.56)	1.16 (0.53)	1.08 (0.29)	1.16 (0.53)	1.10 (0.46)
Median	1.00	1.00	1.00	1.00	1.00	1.00
Q1 ; Q3	1.00; 1.00	1.00; 1.00	1.00; 1.00	1.00; 1.00	1.00; 1.00	1.00; 1.00
Min ; Max	1.0; 5.0	1.0; 6.0	0.8; 6.0	0.5; 3.0	0.8; 6.0	0.5; 6.0

A12. Priority question: Please provide a breakdown of the systemic corticosteroids and/or systemic antibiotics required for the treatment of severe exacerbation events (similar to the information provided for moderate exacerbation events in Table 25, Document B).

Adjudicated severe exacerbation events were treated in a hospitalisation or emergency medical care setting. Treatment with systemic corticosteroid and antibiotic courses were not recorded for these severe events, and so it is not possible to provide the breakdown requested. It is perhaps likely, but cannot be assumed, that these severe exacerbation events were treated with both systemic corticosteroid and antibiotic courses.

Adverse events

A13. Priority question: The occurrence of raised eosinophils is reported as an adverse event in BOREAS (BOREAS CSR, Table 87). The same information is not provided for the NOTUS trial.

a) **Please confirm whether this is because there were no incidences of raised eosinophils for the NOTUS trial;**

There were no events of clinically symptomatic eosinophilia reported in either study. Raised eosinophilia was reported in a very small number of patients in both studies. See below.

b) **If data is available for raised eosinophils in the NOTUS trial, please provide this information for the dupilumab and the placebo group.**

There were instances of raised eosinophils reported as adverse events for both BOREAS and NOTUS. In BOREAS; one patient placebo and 3 patients dupilumab (BOREAS CSR; Table 87; page 240). In NOTUS; one patient placebo and 4 patients dupilumab (NOTUS CSR; Table 85; page 239). Clinically symptomatic eosinophilia was not reported in either BOREAS or NOTUS.

A14. Priority question: Please provide a breakdown of the treatment emergent SAEs and severe TEAEs for the dupilumab and placebo arms in the pooled analysis (similar to the information provided for TEAEs in Table 32, Document B).

Table 32 in Document B is the provided breakdown of the treatment emergent TEAEs for the dupilumab and placebo arms in the pooled analysis. The equivalent tables individually for BOREAS and NOTUS can be found in Appendix S, Tables 12 (page 32) and 14 (page 34).

The equivalent data for participants in the pooled analysis with treatment emergent severe AEs and serious AEs (SAEs) are provided below with the system organ class term. The full table is presented in Appendix 2 including high level and preferred terms.

Table 20. Number (%) of participants with treatment emergent severe AEs and serious AEs (SAEs) by Primary SOC, and HLGT – pooled safety population

PRIMARY SYSTEM ORGAN CLASS	Placebo	Dupilumab
	(N=934)	(N=938)
Treatment emergent severe AEs		
Any Class	[redacted]	[redacted]
INFECTIONS AND INFESTATIONS	[redacted]	[redacted]
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	[redacted]	[redacted]
BLOOD AND LYMPHATIC SYSTEM DISORDERS	[redacted]	[redacted]
IMMUNE SYSTEM DISORDERS	[redacted]	[redacted]
ENDOCRINE DISORDERS	[redacted]	[redacted]
METABOLISM AND NUTRITION DISORDERS	[redacted]	[redacted]
PSYCHIATRIC DISORDERS	[redacted]	[redacted]
NERVOUS SYSTEM DISORDERS	[redacted]	[redacted]
EYE DISORDERS	[redacted]	[redacted]
CARDIAC DISORDERS	[redacted]	[redacted]
VASCULAR DISORDERS	[redacted]	[redacted]
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	[redacted]	[redacted]
GASTROINTESTINAL DISORDERS	[redacted]	[redacted]
HEPATOBILIARY DISORDERS	[redacted]	[redacted]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	[redacted]	[redacted]
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	[redacted]	[redacted]
RENAL AND URINARY DISORDERS	[redacted]	[redacted]
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	[redacted]	[redacted]
INVESTIGATIONS	[redacted]	[redacted]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	[redacted]	[redacted]
Treatment emergent serious AEs		
Any Class	[redacted]	[redacted]
INFECTIONS AND INFESTATIONS	[redacted]	[redacted]
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	[redacted]	[redacted]
BLOOD AND LYMPHATIC SYSTEM DISORDERS	[redacted]	[redacted]
IMMUNE SYSTEM DISORDERS	[redacted]	[redacted]
ENDOCRINE DISORDERS	[redacted]	[redacted]
METABOLISM AND NUTRITION DISORDERS	[redacted]	[redacted]
PSYCHIATRIC DISORDERS	[redacted]	[redacted]
NERVOUS SYSTEM DISORDERS	[redacted]	[redacted]
EYE DISORDERS	[redacted]	[redacted]
CARDIAC DISORDERS	[redacted]	[redacted]
VASCULAR DISORDERS	[redacted]	[redacted]
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	[redacted]	[redacted]
GASTROINTESTINAL DISORDERS	[redacted]	[redacted]
HEPATOBILIARY DISORDERS	[redacted]	[redacted]
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	[redacted]	[redacted]
RENAL AND URINARY DISORDERS	[redacted]	[redacted]
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	[redacted]	[redacted]

PRIMARY SYSTEM ORGAN CLASS	Placebo	Dupilumab
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	[redacted]	[redacted]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	[redacted]	[redacted]

SOC = System organ class, HLGT. n (%) = number and percentage of participants with at least one treatment emergent SAE during the entire TEAE period

Section B: Clarification on cost-effectiveness data

For any scenarios requested in Section B, the EAG requests that all scenarios are implemented as user selectable options in the CEM so that they can be combined if required. Furthermore, if the company updates its base case results following any changes, please ensure that cost-effectiveness results, sensitivity and scenario analyses incorporating the revised base case assumptions are provided with the response along with a log of changes made to the company base case.

The base case has been updated due to model fixes and a change log provided in Appendix 1. The cost effectiveness results from the original CS are provided in Appendix 2. We were unable to implement user selectable options in the CEM in the time available but a sheet has been added to the model [Scenarios_RecommendedbyEAG] with instructions showing how the scenario can be run. We hope this is sufficient for the EAG to be able to conduct their analyses.

Cost-effectiveness literature searches

B1. Please clarify why grey literature searches excluded any studies prior to 2020?

The grey literature search was limited to conference presentations from 2020 onwards as a standard practice. This approach reflects the fact that conference abstracts are not peer-reviewed, and if a study has not been published as a full manuscript within four years, it is typically assumed that it may not have been considered suitable for publication.

B2. Please clarify why oral therapies were excluded from the systematic literature review, despite roflumilast being listed in the NICE scope.

Oral therapies were only excluded from the cost-effectiveness SLRs. This decision was based on the assumption that the costs of oral therapies, would differ significantly from the relevant cost inputs required for the model, given that

dupilumab is administered via subcutaneous injection. Therefore, it was assumed that oral therapies would not be relevant for this analysis. However, due to the appearance in the scope of roflumilast a hand search was conducted to identify specific inputs for Roflumilast.

Model structure and implementation

B3. Priority question: The EAG notes that a one-year cycle length is not in line with the regularity of dupilumab administration and may not capture the timings of key clinical events. This may be the case if the treatment effect maintenance period of dupilumab lasts for a shorter time period than used in the base case. For example, the company's structured expert elicitation suggests that time to decline would be 6.6 months but due to the use of an annual cycle length the scenario analysis was rounded to 1 year. The EAG notes that in the previous appraisal for roflumilast, a cycle length of one month was used and accepted by the committee as appropriate. Please demonstrate that the one-year cycle length captures all relevant events and accounts for them appropriately or please adapt the model to use a one-month cycle length (which would be the EAG's recommendation).

The use of a one-year cycle length is appropriate for this submission for several reasons. First, the impact of an exacerbation on a patient's quality of life can persist for several months,(8) making an annual cycle length suitable to capture the long-term consequences of these events. Additionally, the efficacy response criteria for dupilumab are based on the number of exacerbations that occurred in the year prior and the review period in real clinical practice is likely to be annually. The Whittaker et al. 2022 exacerbation rated used in the model as the source for transitions related to exacerbations used the prior year to predict the risk of future exacerbations, reinforcing the appropriateness of a one-year cycle length. Evidence shows that exacerbations have a seasonal component, with more occurring during the winter period. A one-year time period ensures that all patients experience all parts of the annual season, so all and any triggers for their exacerbations are included in the annual cycle length. Furthermore, a shorter cycle length would require the use of tunnel states and add complexity to the model. As such, a one-year cycle length

aligns with the time frame of the clinical data and is more relevant for modelling the treatment effect.

Regarding the structured expert elicitation's FEV_1 treatment effect duration results, It would of course, be unreasonable to assume that FEV_1 remains constant throughout the model horizon but given active inhibition of IL4/13 and the known good adherence to dupilumab whilst on treatment, (which is not the case for inhaled therapies in COPD), an extended treatment effect period beyond the 52-week trial period is included in the model. The structured expert elicitation exercise carried out to elucidate this unobservable quantity of time to FEV_1 decline provided an aggregate result of 6.601 months (95% CI: 0.700, 24.690), after round 2 but 9.058 months (95% CI: 0.627, 39.383) in the first round when experts were not aware of their colleagues' answers. In round 2 after seeing the other responses they had a chance to alter their responses.

We appreciate that neither 6.6 nor 9.1 are commensurate with the model cycle length however we do not believe it is unreasonable to round this to 1 year (used in sensitivity analysis) given the data from TRAVERSE (see question B17) and the mode of action for dupilumab. It is worth noting that the aggregate results were constrained to be below 1 year by the answer of only one expert who categorically stated that there would be no time to decline. This is contrary to the observed data in TRAVERSE and the observation in the clinical trial that dupilumab causes an FEV_1 improvement within 2 weeks which is sustained whilst on treatment. Generally, the experts suggested trial and treatment effects may be maintained for some time, most likely due to reduction in exacerbation rates.

Furthermore, while the EAG referenced the one-month cycle length used in the Roflumilast submission, it is important to note that this was deemed appropriate in that case because half-cycle corrections were not applied due to the short cycle length. In contrast, our submission uses a one-year cycle length and appropriately applies half-cycle corrections to ensure accurate modelling of clinical events over time.

B4. Priority question: A decision tree was used to represent the 52 week trial period. Typically, time is not explicitly modelled in decision trees. As noted by

the company, beyond the initial two weeks increase in patients FEV_1, this was observed to remain stable in both treatment arms. Please clarify why the decision tree did not just use data on baseline to 52 weeks instead of the baseline to 2 weeks and then 2 weeks to 52 weeks in the first year of the model?

The decision tree structure was designed to replicate the trial as closely as possible. By separating the initial baseline-to-2-week period from the 2-week-to-52-week period, the model accurately reflects the observed rapid increase in FEV_1 during the first two weeks, followed by its stabilisation over the remainder of the trial. This approach is particularly important because, while stabilisation of FEV_1 from 2 to 52 weeks may be observed, we did not want to assume this pattern in advance. By modelling both the 0-2 week and 2–52-week periods based on the data rather than assumptions, the model ensures it appropriately captures the unique treatment response patterns observed in the clinical trial data.

B5. Priority question: In order to obtain updated deterministic results following any changes made to the model, a macro is required to be run. This means that any changes made are unable to easily be undone. Please update the model to provide the deterministic results without the use of a macro.

The model has been updated by removing the macro and creating treatment-specific engines to run deterministic analyses. The treatment specific engines are included as separate tabs in the model and are named as Markov_Engine_1, Markov_Engine_2, and so on (until Markov_Engine_7)

B6. In the 'Markov_engine' model sheet, the first row (row 35) is said to correspond to the distribution at the end of the trial period. However, the age is set to 65. If patients are 65 at the beginning of the trial then by the end of the decision tree period (52 weeks) they should be 66. Please clarify if this is correct and amend the model as necessary.

We thank ERG for this comment, and we apologize for the error. The first row corresponds to the distribution at the end of the trial period and the age must be set to 66 (1 year after the trial start) instead of 65. This has been amended in the updated model. The changes made ensures the following:

- Starting age of patients in the Markov engine is 66 (cell I35)

- General population utility of patients in the first cycle of Markov corresponds to patients who are 66 years old (cell MD35)

B7. Discounting should not be implemented in the first year of the model; however, in the 'Markov_engine' model sheet, discounting is being applied for costs and utilities (columns F and G) from the model cycle corresponding to the trial period (baseline to 52 weeks). Please amend this error in the model so that discounting is only applied from year 1 onwards.

We have modified the discount rate to start in 'Year 1' in the Markov portion of the model. See the [Markov_Engine_x] work sheets in Cells [F35:G35] which drive year 0 calculations. These now show a discount rate of 1. All cells below have been updated to reflect discounting from year 2 overall (ie at the start of the Markov model).

All model results provided in this response include this adapted discounting schedule. As expected, there is a very slight decrease in the ICERs.

B8. Please clarify why in cell H35 of 'Markov_engine', time in weeks at end of cycle is 0 whereas time in years at end of cycle (cell I35) is 1? If this is an error, please amend the model.

Column H represented time in weeks from the start of the Markov period and column I from model start, including the trial period. Column H did not have any dependencies in the original model and has now been removed to avoid any further confusion.

B9. The EAG notes that the PSA does not account for correlation between parameters in the regression models used to derive health state utility values. Please clarify why this was not implemented and explain any measures that have been taken to avoid inconsistencies in sampled values.

Although the correlation between parameters in the regression model was not accounted for when running PSA, the covariance is very low and is not expected to have substantive impact in the PSA.

Covariance matrices are attached for the models with all covariates (Model 1) and with only statistically significant covariates (Model 2).

Baseline parameters

B10. Priority question: In the first 52 weeks of the economic model, depicted using the decision tree to replicate the trial period, data from each treatment arm is used directly for outcomes at 2 and 52 weeks. Please clarify why pooled data from all patients was used to inform the proportion of patients in each GOLD stage health state at baseline as opposed to treatment arm specific. In addition, please incorporate a scenario analysis in the model that uses the baseline GOLD stage proportions at baseline specific to each treatment arm.

We thank the EAG for the comment. Firstly, the % of patients at baseline by COPD stage has been updated due to an earlier error (Appendix 1). The updated model has the flexibility to consider the GOLD stage proportions at baseline specific to each treatment arm as a scenario. A dropdown allows the user to incorporate the treatment-specific % at baseline as opposed to using the baseline proportions with the combined dupilumab + background therapy and background therapy arms.

Table 21. EAG scenario results for question B10

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Deterministic							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,530
Background Therapy	[redacted]	[redacted]	[redacted]				
Probabilistic							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,862
Background Therapy	[redacted]	[redacted]	[redacted]				

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Treatment effectiveness

B11. Priority question: The company notes that exacerbations are often lower in a clinical trial setting than in real-world clinical practice and therefore use the annual rate of exacerbations based on those observed in the year prior to trial randomisation. The trial data showed an increase in FEV_1 in both treatment arms at the beginning of the trial period, which appeared to be maintained up to week 52, with this declining for patients on placebo post 52 weeks. Clinical experts to the EAG noted that this increase observed in the placebo arm is also likely due to the trial setting and the optimising of

treatment. In addition, clinical experts stated that during the COVID-19 pandemic, patients had lower exacerbation rates and higher FEV_1 due to viral shielding which may also account for increases in FEV_1 observed in both treatment arms in the trial period.

a) **Please clarify why only exacerbations have been assumed to differ in a clinical trial setting and not patients FEV_1?**

We acknowledge and agree with the EAG's observation regarding the potential trial effect on FEV_1. Our rationale was that using baseline FEV_1 data from the trial allowed us to retain as much trial data in the model where possible.

Given that exacerbations were the primary endpoint for our trials, we focused on ensuring they were accurately represented while accounting for any trial effect. For results that consider the trial effect on FEV_1, please refer to Table 22.

b) **Please include a scenario analysis in which the distribution of patients in each GOLD stage for the placebo arm at 52 weeks (and the start of the Markov model) is informed by the distribution at trial baseline to remove any 'trial effects'. As it is expected that patients in the dupilumab arm will also experience the same 'trial effects' as those on placebo, for the dupilumab arm please use the baseline distribution with the "treatment effect" applied, in which the "treatment effect" is the difference between the observed dupilumab treatment effect and the observed placebo treatment effect.**

The result for the depicted scenario is provided below. This scenario was implemented by applying the same distribution of patients at the end of the FEV_1 amelioration phase to the distribution at the end of the FEV_1 maintenance phase (Week 52), while preserving the treatment effect. Since the treatment effect on FEV_1 is captured only by the percent of patients by COPD stages, the treatment effect of dupilumab is applied as an 'incremental effect' to the percent of patients on background therapy by COPD stages. In order to ensure the percent of patients by COPD stage sums up to a 100%, the proportion of patients in very severe COPD is calculated in a restrictive fashion. Please refer to the 'trial period' tab in the cost-effectiveness model for further information.

Table 22. EAG scenario results for question B11b

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Deterministic							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,811
Background Therapy	[redacted]	[redacted]	[redacted]				
Probabilistic							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,635
Background Therapy	[redacted]	[redacted]	[redacted]				

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

B12. Priority question: Table 17 of the efficacy CSR shows that there was no statistically significant difference in severe exacerbations between the two treatment arms in the 52-week trial period. However, as the treatment effect is modelled based on the rate ratio of the rate of annual exacerbations observed in each treatment arm split between GOLD severity level, a difference in severe exacerbations is modelled for the lifetime of patients, while they remain on dupilumab. Please include a scenario analysis where there is no difference in severe exacerbations between treatment arms.

While we understand the concerns raised, it is worth noting that the BOREAS and NOTUS studies were not powered to measure dupilumab versus placebo differences in the rate of severe exacerbation reduction. Also, the number of severe exacerbation events observed during the trials (similarly to other phase 3 COPD studies, such of those for triple inhalers) was perhaps lower (across both arms) than might be expected in real world clinical practice in the pre- or post-COVID era (as has been demonstrated by the exacerbation rates observed in our HES database analysis which examined patients meeting the BOREAS inclusion criteria). The low number or severe exacerbation events in BOREAS and NOTUS will have impacted the statistical power to detect significant differences. This limitation should be taken into consideration and put in the context of what might be expected in clinical practice, when interpreting the results.

Additionally, there are multiple reasons to believe that the annualised severe exacerbation reduction achieved in the pooled analysis is an accurate reflection of the actual benefit of dupilumab versus placebo:

- The time to first severe COPD exacerbation compared to placebo (a clinically significant measure) was statistically significant. Figure 18 in the CS shows that dupilumab significantly delayed time to first severe COPD exacerbation compared to placebo, reducing the risk of first severe COPD exacerbation by 39% (HR: 0.611; 95% CI: 0.409, 0.912; nominal p=0.0160).

- In the analysis of the pooled data for all severe adjudicated exacerbation events occurring during the on-treatment period (from initiation to end of treatment or last dose + 16 days) for participants who have opportunity to reach Week 52 there was a statistically significant difference in the rate of severe exacerbations between the dupilumab and placebo arm. The results for this analysis are shown in Table 23 below.

Table 23. Analysis of the annualized rate of severe COPD exacerbations during on-treatment period. Pooled ITT population with an opportunity to reach Week 52.

During on-treatment period	Placebo (N = 830)	Dupilumab (N = 830)
Number of participants with >=1 severe exacerbation event		
Number	830	830
No	[redacted]	[redacted]
Yes	[redacted]	[redacted]
Total number of severe exacerbation events	[redacted]	[redacted]
Total patient-years followed	[redacted]	[redacted]
Unadjusted annualized severe exacerbation event rate[a]	[redacted]	[redacted]
Adjusted annualized severe exacerbation event rate[b]		
Estimate (95% CI)	[redacted]	[redacted]
Relative risk vs. placebo (95% CI)		[redacted]
P-value		[redacted]
Risk difference vs. placebo (95% CI)[c]		[redacted]

[a]The total number of events that occurred during on-treatment period divided by the total number of patient-years followed in on-treatment period.
[b]Derived using negative binomial model with the total number of the events occurring during on-treatment period as the response variable, and treatment group, study, region (pooled country), ICS dose, smoking status at screening, baseline disease severity, and number of moderate or severe COPD exacerbation events within one year prior to the study as covariates, and log-transformed treatment duration as an offset variable.
[c]Derived using delta method.

- The p-value for the comparison of severe exacerbations in the ITT population (p=0.07) was very close to the conventional threshold for significance (p=0.05) and therefore carries nearly the same level of confidence.

- The 95% confidence interval for the annualised rate of severe exacerbation rate ratio, which narrowly crossed 1 (0.438 to 1.037) with a point estimate of 0.674, indicates a strong trend favouring dupilumab treatment.

- The magnitude of reduction observed is consistent for both moderate and severe exacerbations. UK expert clinical opinion indicated that the triggers and mechanisms for both moderate and severe exacerbations are deemed broadly similar, differing mostly in magnitude. Indeed, there is nothing pathophysiologically different between moderate or severe exacerbations and the distinction is largely in the setting of care. This suggests that whilst the absolute number of exacerbations will be different between moderate and severe, the rate reductions for both would be expected to be similar.

- Dupilumab versus placebo benefits are seen across multiple other outcomes, that are consistent with, and might be expected given, the association between severe exacerbations and lung function, symptoms and QoL.

It would be wholly inappropriate to assume or consider that the severe exacerbation reduction with dupilumab may be zero. This view is supported by numerous UK clinical experts who expressed their opinion to us.

Nonetheless we provide the requested analysis setting the exacerbation rate to be the placebo rate in both arms.

Table 24. Results for the analysis in which there is no difference in severe exacerbation rate.

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Deterministic							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£61,457
Background Therapy	[redacted]	[redacted]	[redacted]				
Probabilistic							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£55,427
Background Therapy	[redacted]	[redacted]	[redacted]				

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

B13. Priority questions The EAG notes that the rate ratio calculated for very severe COPD patients who are dupilumab responders with severe

exacerbation appears to be incorrect and notes that this should be 0.29 (0.02/0.07). Please clarify why 0.18 has been used in the economic model?

No severe exacerbation was reported for patients fitting GOLD grade 4 criteria in the dupilumab arm. Therefore, the relative risk 0.18 (0.02/0.11) for severe COPD patients was assumed. We have also added a note in the model to clarify this. Please find the unadjusted annualised severe exacerbation event rates below.

Table 25. Unadjusted annualised severe exacerbation event rate from the pooled ITT population with an opportunity to reach Week 52

During on-treatment period (from week 2 to EOT)	GOLD Grade 1 (N=92)		GOLD Grade 2 (N=811)		GOLD Grade 3 (N=642)		GOLD Grade 4 (N=64)	
	Placebo (N=34)	Dupilumab (N=56)	Placebo (N=409)	Dupilumab (N=388)	Placebo (N=323)	Dupilumab (N=292)	Placebo (N=32)	Dupilumab (N=28)
Total patient-years followed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unadjusted annualized severe exacerbation event rate[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

This may be a conservate approach. An alternative would have been to combine GOLD 3 and 4 (0.02/0.18) for relative risk of 0.11.

B14. In the economic model, the standard errors associated with the exacerbation rates observed in the trial are currently an assumption. Please clarify why these are based on assumptions and not derived from the statistical analysis?

The unadjusted annualised exacerbation rates observed in the trial were used directly as inputs in the economic model. As these rates were used in their raw form, without adjustment for covariates, the 95% Cl were not calculated as part of this approach.

However, to address this, a negative binomial model has since been conducted, which accounts for the distribution of exacerbation rates and provides the associated 95% Cl limits. The results of this analysis are provided below for your reference. The 95% CI from the negative binomial model (and the normally approximated SE-s) has been implemented in the revised model and are used in the updated PSAs.

Table 26. Moderate or severe COPD exacerbations during on-treatment period from Week 2 to EOT according to GOLD severity at Week 2

During on-treatment period (from week 2 to EOT)	GOLD Grade 1 (N=92)		GOLD Grade 2 (N=811)		GOLD Grade 3 (N=642)		GOLD Grade 4 (N=64)	
	Placebo (N=34)	Dupi (N=58)	Placebo (N=409)	Dupi (N=402)	Placebo (N=323)	Dupi (N=319)	Placebo (N=32)	Dupi (N=32)
Total number of moderate or severe exacerbation events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total patient-years followed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unadjusted annualised moderate or severe exacerbation event rate[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unadjusted rate (95%CI) derived from negative binomial model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

All moderate or severe adjudicated exacerbation events occurred during the on-treatment period (from week 2 to end of treatment or last IMP + 16 days) are included.

[a] The total number of events that occurred during on-treatment period divided by the total number of patient-years followed in on-treatment period.

Long-term FEV_1 and exacerbation rates

B15. Priority question: Beyond the trial period, the company uses Fenwick *et al.* 2021 to inform transition probabilities between COPD health states and applies a modifier to account for a faster rate of decline for patients with Type 2 inflammation. The transition probabilities reported in Fenwick *et al.* have been derived using baseline characteristics for age, percentage male and height of the population being assessed in Fenwick *et al.* in order to estimate the decline in FEV_1 percent predicted. Therefore, these transition probabilities are specific to the population modelled in Fenwick *et al.* On page 130 of the CS, the company state that, "We have applied this modifier as well as the average patient age and height at baseline from the pooled BOREAS and NOTUS trials to the transition probabilities reported by Fenwick et al. 2021". Please provide further details of the exact calculations and adjustments that have been made to the Fenwick *et al.* transition probabilities in order to derive those presented in Table 50 of the economic model.

The detailed calculations are presented in the 'Fenwick inputs' tab in the model.

- Step 1: The FEV_1 predicted for the age-matched population (column D and U) was calculated from the equation using height and age (Table 6 in Quanjer et al. 1993). A “typical” patient was defined by the characteristics of the trial population (cell C11 and C12) and assumed to currently be at the mid-point of the severity category (i.e., 65% FEV_1 predicted for moderate COPD and 40% FEV_1 pred for severe COPD; cell F15 and W15). These values were used to estimate the starting FEV_1 predicted for a “typical” patient with and without exacerbation (cell I17, J17, Z17, AA17).

- Step 2: In Fenwick et al. 2021, the slope coefficient (-40.9) refers to an annual decline of 40.9 mL in FEV_1 for individuals with no recent history of an exacerbation. This was based on a regression equation fit to the data from the TORCH study. The coefficient for recent exacerbation history (-30.6) reflects the additional decline in FEV_1 mL for those individuals with a recent exacerbation (within the last year). These values along with the ratio (1.52) of the rate of decline for the EOS ≥300 cells/μL group compared to the overall cohort rate (details presented in Section B.3.3.6.2) were used to estimate the annual decline in FEV_1 mL (cell I15, J15, Z15, AA15). Then the FEV_1 predicted for a “typical” patient after first year were derived (column I, J, Z, AA). The FEV_1 % predicted were calculated in column F, G, W, X.

- Step 3: These values were used to calculate the time taken for a “typical” patient in each COPD severity category to cross the threshold to the next severity category (i.e., 50% for severe and 30% for very severe, cell C14 & T14). The time in years until the next severity category is reached was derived with the application of the annual reduction (cell G8-9, X8-9). The estimated time was then converted to a transition probability assuming an exponential distribution over time (cell J8-9, AA8-9).

B16. Priority question: Table 47 of the CS shows the reference rates for moderate and severe exacerbations by GOLD severity for patients who had no previous exacerbations. The sources for this table are both Whittaker 2022 and

Wallace 2019. Please clarify exactly what data were used from Wallace and how these rates have been derived.

The reference moderate and severe exacerbations rate in patients with EOS≥300 cells/µL reported in the Whittaker et al 2022 paper are for all patients and are not stratified by GOLD stage. To derive the reference exacerbation rates by GOLD stage, the overall rates from Whittaker 2022 were adjusted using the relative risks reported in Wallace et al. 2019.

Table 2 from Wallace et al. (2019) presents the distribution of patients by GOLD stage, along with the crude rates of severe and moderate exacerbation events per 100 person-years for each GOLD stage. These crude rates were utilised to calculate the relative rates. The relative risk, as determined by Wallace et al. (2019), was employed to compute the weighted average relative risk, taking into account the patient distribution by GOLD stage from Whittaker et al. This weighted average was then used to establish the baseline rate of moderate or severe exacerbations, stratified by GOLD stage. This approach allowed the stratification of exacerbation rates by GOLD severity, enabling the data to be used in the model. For detailed calculations, please refer to Appendix 4, which contains the relevant Excel spreadsheet.

B17. Priority question: The company uses the open-label extension study (TRAVERSE) from dupilumab in moderate/severe asthma patients to inform the 'maintenance period' of the treatment effect for dupilumab in COPD patients (three years from treatment start). The EAG notes that these patients were considerably younger on average compared to the dupilumab COPD trials (48.2-51.7 years versus 65) and had higher pre-bronchodilator FEV_1 at baseline than patients with COPD. Clinical expert advice to the EAG suggests that COPD patients treated with dupilumab would decline more quickly than asthma patients due to these observed differences. Please justify the 3-year period in light of this?

Lung function decline is an expected part of the ageing process. However, even studies of nonpatients (respiratory disease excluded) indicate that a risk factor for increased decline is the presence of Type 2 inflammation, suggesting that some components of decline may not be "normal". We do however accept that a certain

degree of lung function decline will occur as people simply age, including those with COPD. However, the rate of decline, as measured in most studies, is a constant (or near constant) rate between the ages of 40 and 70.(9) Therefore, we do not agree the age difference between asthma patients in TRAVERSE and COPD patients in BOREAS and NOTUS would impact on decline rate, and the decline magnitude (per year) would likely be smaller for patients with COPD (due to lower absolute FEV_1). Fenwick (2021) has calculated transition similar probabilities for patients moving from mild (FEV_1 ≥80%) to moderate (FEV_1 50-79%) and moderate to severe (FEV_1 30-49%). Patients moving from severe (FEV_1 30-49%) to very severe (FEV_1 <30%) do so however at higher risk. Therefore, for the most part, we do not agree that the starting FEV_1 difference between asthma patients in TRAVERSE and COPD patients in BOREAS and NOTUS would impact significantly on decline rate.

Lung function decline in both asthma and COPD is associated with common mechanisms including airway wall remodelling, altered airway compliance, and mucus hypersecretion,(10, 11) associated with Type 2 inflammation (emphysema is a driver of lung function decline only in COPD). By targeting Type 2 cytokine signalling by IL-4 and IL-13, evidence indicate that dupilumab positively impacts lung function by reducing fibrosis and airway thickening (airway remodelling), reducing airway contractility (airway compliance) and airway resistance and reducing air trapping (mucus). Such functions may be considered part of the “mechanism of action” of dupilumab in the lung, under the influence of chronic Type 2 inflammation. Indeed, the recently published VESTIGE study of dupilumab versus placebo in the treatment of asthma quantified reduced airway inflammation and mucus plugging, leading to improved airway volume and flow.(12) Such benefits may be considered part of the “mechanism of action” of dupilumab in the lung, under the influence of chronic Type 2 inflammation, and would be reasonably postulated to be applicable to the treatment of both asthma and COPD. Additionally, an exploratory investigation of lung function in the asthma QUEST study, where the trajectory of FEV_1 from week 4 to 52 was measured (excluding the initial improvement in FEV_1), suggested that while placebo treated patient’s lung function decreased by approximately 40 mL over a year, those patients treated with dupilumab experienced no decrease.(13) This reported dupilumab protection from lung function decline in asthma patients is being investigated further in the long-term phase 4 ATLAS study. In summary, the

maintenance of lung function in TRAVERSE over 3 years of treatment with dupilumab is supported by the mechanism of action of dupilumab on lung airways, both for initial increases and sustained improvement. We have modelled lung function decline to begin after 3 years – the end of TRAVERSE data - but there is no reason to think that the benefit would not be maintained past 3 years if dupilumab treatment was to continue.

We have provided a subgroup analysis of the TRAVERSE study in which the population of patients from parental studies (DRI12544 and EFC13579) has been matched to the pooled BOREAS and NOTUS data, based on parent study baseline parameters, acknowledging the EAG comments. A simple exploratory matching exercise using the Matching Adjusted Indirect Comparisons (MAICs) methodology was carried out on age and pre BD FEV_1 (on both mean and standard deviations) with no preselection of patients. To ensure comparability of the population at baseline, age and pre-BD FEV_1 were weighted in the TRAVERSE population to match to the baseline characteristics of the pooled BOREAS and NOTUS studies. Before matching, the sample size was 2062, and after matching the effective sample size (ESS) was 533. A comparison of the Age, Gender, BMI and lung function baseline characteristics before and after matching is tabulated below. (

Table 27). As can be seen, the populations before and after matching are similar (other than age and FEV_1) in BMI and mean blood EOS counts but differ in a slightly higher female proportion after matching. Compared to the pooled BOREAS and NOTUS populations, the matched TRAVERSE population is similar in all these parameters, other than the higher proportion of females in the TRAVERSE population.

Table 27. Comparison of baseline Age, Gender, BMI and lung function characteristics in TRAVERSE study (patients enrolled in parental DRI12544 and EFC1379 studies) before and after matching on the patient characteristics in the BOREAS/NOTUS studies

Characteristic	TRAVERSE, matching on age (Mean 65.1 y, SD=8.2) and pre-BD FEV_1 (Mean 1.33L, SD = 0.48)		Pooled BOREAS and NOTUS
	Before matching (N = 2062)	After matching (ESS = 533.16)	
Mean Age (years)	[redacted]	[redacted]	[redacted]
Male (%)	[redacted]	[redacted]	[redacted]
Female (%)	[redacted]	[redacted]	[redacted]
Mean BMI (kg/m^2)	[redacted]	[redacted]	[redacted]
Mean Baseline pre-bronchodilator FEV_1 (L)	[redacted]	[redacted]	[redacted]
Mean Blood EOS (giga/L)	[redacted]	[redacted]	[redacted]

The mean pre-bronchodilator FEV_1 and % predicted FEV_1 over the 96 weeks of TRAVERSE, before and after matching, is represented in the figures below. (Figure 5 and Figure 6) Note that the parent study baseline FEV_1 was measured 52 weeks prior to the TRAVERSE baseline for the majority of patients (those rolling over from the QUEST study), but has been represented at “-2 weeks” on these graphs for simplicity. Also, the FEV_1 change over time for the 52-week duration of the parent studies (involving both placebo and dupilumab treatment arms) has not been represented.

Figure 5 Comparison of mean pre-BD FEV_1 between TRAVERSE and TRAVERSE matched on age (Mean 65.1 y, SD=8.2) and pre-BD FEV_1 (Mean 1.33L, SD = 0.48)

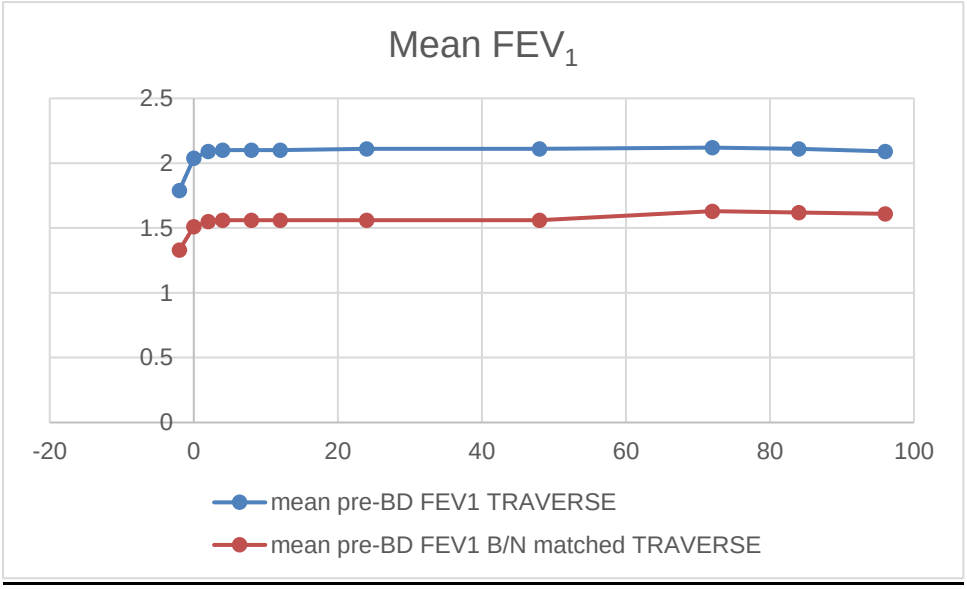
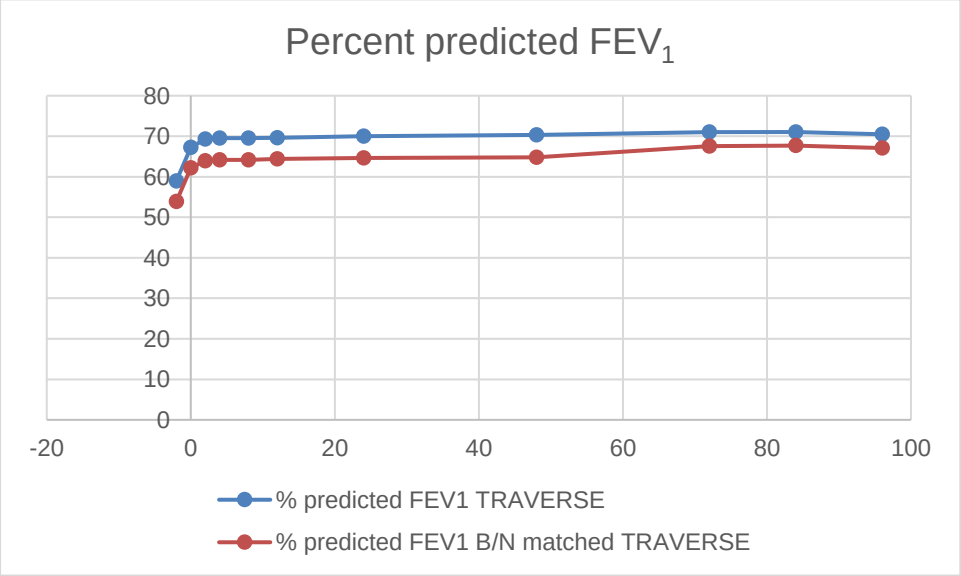


Figure 6. Comparison of mean percent predicted FEV_1 between TRAVERSE and TRAVERSE matched on age (Mean 65.1 y, SD=8.2) and pre-BD FEV_1 (Mean 1.33L, SD = 0.48)



The older and lower FEV_1 patients in the TRAVERSE population matched to BOREAS/NOTUS exhibited a lower magnitude of benefit with dupilumab treatment, compared to the full TRAVERSE population, but the stability of this FEV_1 benefit over the 2 years of TRAVERSE (plus 1 year, for patients treated with dupilumab in parent studies) remains consistent. This was also true when considering percent predicted FEV_1 rather than mean absolute values.

This matched adjusted data suggests no increased rate of lung function decline for asthma patients based on an older age and poorer lung function equivalent to that of COPD patients, contrary to that postulated by the EAG clinical expert.

Overall, we maintain that a 3 year 'maintenance period' of the FEV_1 treatment effect for dupilumab in COPD patients (three years from treatment start) is appropriate. This is supported by the TRAVERSE data in asthma patients, the similarity of lung function decline drivers in both asthma and COPD, and the mechanism of action for dupilumab in addressing lung function detriment and protection from decline.

B18. Please include an additional scenario analysis in which patients on dupilumab begin to experience FEV_1 decline at the end of the 52 weeks trial period, as is modelled for the background therapy only arm (i.e. no maintenance period).

Table 28. EAG scenario results for question B18

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Deterministic							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,488
Background Therapy	[redacted]	[redacted]	[redacted]				
Probabilistic							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,914
Background Therapy	[redacted]	[redacted]	[redacted]				

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

B19. For those patients who 3 or more exacerbations, trial data is used to inform the average number of exacerbations (moderate = 3.84, severe = 3.75). Please clarify the exact data that was used from the post-hoc analyses to calculate these averages.

The data that was used from the post-hoc analyses to calculate these averages is presented in Table 29 below.

Table 29. Number of moderate exacerbation events from the pooled ITT population with an opportunity to reach Week 52

During on-treatment period	Placebo (N=830)	Dupilumab 300 mg q2w (N=830)
Number of moderate (without severe exacerbations) and exacerbation events		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]

Median	[redacted]	[redacted]
Q1 ; Q3	[redacted]	[redacted]
Min ; Max	[redacted]	[redacted]
Sum	[redacted]	[redacted]

The average number of moderate exacerbations in patients with at least 3 moderate exacerbations, was calculated based on a weighted average between the two arms 3.84 (=(3.8*66+3.9*37)/(66+37)).

Table 30. Number of severe exacerbation events from the pooled ITT population with an opportunity to reach Week 52

During on-treatment period	Placebo (N=830)	Dupilumab (N=830)
Number of severe exacerbation events		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1 ; Q3	[redacted]	[redacted]
Min ; Max	[redacted]	[redacted]
Sum	[redacted]	[redacted]

The average number of severe exacerbations in patients with at least 3 severe exacerbations, was calculated based on a weighted average between the two arms 3.75 (=(4*2+3.5*2)/(2+2)).

CV events

B20. In the decision tree used to represent the trial period, the company includes non-fatal CV events, assumed to differ by trial arm. This is stated to be based on a difference in non-fatal CV events observed in the clinical trials (0.7% versus 1.7%).

a) The 'Summary Safety Pooled analysis BOREAS+NOTUS CSR' document suggests that these proportions include fatal cardiovascular events despite the CS stating that these proportions represent non-fatal CV events. Please clarify if the proportions used in the model also include fatal CV events.

We are grateful to the EAG for picking up this inconsistency. The proportions used in the model should include only non-fatal events. In total the proportion of CV events for MACE including fatal events was lower for dupilumab than for placebo [0.7% versus 1.7%]. We have updated the model to account for a sub-set of these events including only non-fatal events. 0.53% (5 non-fatal CV events) is used for the dupilumab + background therapy arm and 1.28% (12 non-fatal CV events) for background therapy alone.

b) In addition, the CSR shows that there was not a statistically significant difference between the two treatment arms ("*The incidence rate for MACE was lower for dupilumab than for placebo [0.7% versus 1.7%], with a risk*

difference of -0.97% [95% CI: -1.96% to 0.03%"]). Please include a scenario analysis where there is no difference in CV events between treatment arms.

A scenario has been run to exclude CV events from the model, i.e., assuming 0% of CV events for both dupilumab and background therapy . The results are presented in Table 31 below.

Table 31. Scenario results including no difference between event rates for non-fatal CV events.

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Deterministic							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,638
Background Therapy	[redacted]	[redacted]	[redacted]				
Probabilistic							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,866
Background Therapy	[redacted]	[redacted]	[redacted]				

c) ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

B21. In the dupilumab trial inputs sheet in the economic model, the percentage of annual CV events in cells N679:670 differs from those listed in the CS (0.9% and 1.9% versus 0.7% and 1.7% quoted). Please clarify why there is the discrepancy?

Thank you for raising this issue. The values in the dupilumab trial inputs sheet under CV events were not linked to any calculated fields so we have now removed them in the updated model. We have also updated the model base case with the correct CV event incidence: 0.53% for the dupilumab + background therapy arm and 1.28% for the background therapy alone.

Mortality

B22. Priority question: The company applies an excess mortality rate compared to the general population, based on GOLD severity, as well as an additional case fatality rate (CFR) of 15.6% for every severe exacerbation.

a) The SMRs calculated by Whittaker *et al.* 2024 controlled for a number of patient baseline characteristics as well as previous exacerbations and airflow obstruction. As patients with more severe COPD have been shown to have higher rates of severe exacerbation, the EAG considers that including a separate CFR may double count the increased mortality rate already associated with each higher stage of COPD. Therefore, please

provide a scenario analysis that does not include a CFR for severe exacerbations.

The EAG have noted that the SMRs published in Whittaker 2023 used in the model to calculate mortality are taken from the 'all-cause' source in the publication and include COPD related, CV death and other.(14) Whilst the publication states that analyses are adjusted by exacerbation the authors do not provide the corresponding HRs so we recognise that these SMRs may include exacerbation risk and understand that the request to provide a scenario analysis that does not include a CFR for severe exacerbations has been made to avoid double counting. Given the importance of this question, we have provided an in-depth answer with some alternatives to the originally proposed base case approach.

SMR source and applicability without modification.

It is critically important to recognise that the SMRs published in Whittaker were calculated from a cohort of patients on standard of care from the HES/ONS data up to 2020. This was at a time when only dual and triple therapies were the predominant treatment strategy, and no biologics (including dupilumab) were available for COPD treatment.

Severe exacerbations resulting in hospitalisation are well known to be strongly predictive of mortality. For example, the IMPACT study which was a 52-week phase III trial that compared the efficacy, safety, and tolerability of triple (ICS/LAMA/LABA) versus double (ICS/LABA or LABA/LAMA) therapy demonstrated a 41-fold increased risk of mortality during a severe COPD exacerbation compared with the exacerbation free period, and a 2-fold increased risk during 1–90 days post resolution.(15)

Dupilumab has been shown to reduce the annualised rate of moderate or severe exacerbations compared to placebo by 31% in the pooled analysis of BOREAS and NOTUS (rate ratio: 0.69; 95% CI: 0.60, 0.79; nominal p<0.0001). Dupilumab has also been shown to improve lung function symptoms, and quality of life:

- Pre-BD FEV_1: Week 12 (147 mL vs. 64 mL; LS mean difference: +83 mL; 95% CI: 53, 112; nominal p<0.0001). Week 52 (133 mL vs. 59 mL; LS mean difference: +73 mL; 95% CI: 40, 107; nominal p<0.0001) vs placebo

- E-RS: COPD total score at Week 52 compared to placebo (LS mean difference: −0.9; 95% CI: −1.4, −0.4; nominal p=0.0006)
- SGRQ: LS mean difference vs placebo: −3.4; 95% CI: −5.0; −1.8; nominal p<0.0001).

All these improvements in outcomes from dupilumab add-on to current treatment mean that a different mortality risk should apply to dupilumab treated patients compared to those treated with current standard of care in Whittaker. Removing the CFR which accounts for the benefit in severe hospitalised exacerbation due to dupilumab treatment from the calculation of mortality in the model is therefore problematic for 2 key reasons:

1. Treatment with dupilumab plus standard care is not the same as treatment with standard care alone so the SMRs from Whittaker are not solely applicable to both arms in the model.

2. Removing the CFR from the model has the effect of removing any benefit due to the proven decrease in moderate and severe exacerbations with dupilumab treatment.

Estimation of the incremental mortality benefit due to dupilumab

BOREAS and NOTUS were not powered on a mortality endpoint and so very few death events were recorded. Consequently, the direct calculation of a mortality hazard ratio is not possible from the dupilumab data. An alternative is to find a proxy for the incremental mortality benefit due to the addition of another active therapy to established treatment in COPD.

The GOLD 2025 guidelines recommend escalation to triple therapy with ICS for patients with COPD who continue to experience exacerbations despite being on dual therapy (LABA/LAMA) or those with persistent symptoms.(16) This recommendation was made as the triple combination has been shown to improve lung function, symptoms, and health status as well as decrease exacerbations compared with dual or monotherapy. It should be noted that the recently published GOLD 2025 guidelines explicitly state dupilumab is the treatment of choice for patients with EOS ≥300 cells/µL as add-on to triple therapy.(16)

On the basis that dupilumab also showed improvements in exacerbation frequency, lung function, symptoms and health status in the pivotal trials as add-on triple therapy, the uplift in treatment effect from ICS add-on to double therapy may be considered analogous to the addition of dupilumab to triple therapy. Evidence exists in the literature to support this.

A Bayesian network meta-analysis published in 2019 which compared exacerbations, mortality, and adverse events according to the drug class found that LABA/LAMA vs ICS/LABA/LAMA increased the risk of death by 32% (odds ratio [OR], 1.32 [95% credible interval, 1.05 to 1.66].(17)

More recently the IMPACT study mentioned earlier sought to examine the relative benefits of triple therapy compared with dual therapy. The primary outcome in the study was the rate of moderate or severe exacerbations, but other outcomes including mortality were also collected.

In IMPACT the rate ratio for moderate or severe exacerbations for ICS/LABA/LAMA vs LABA/LAMA was 0.75; (95% CI, 0.70 to 0.81; 25% difference; P<0.001) and in the most recent post hoc analysis for mortality outcomes the hazard ratio was 0.72 (95% CI, 0.53–0.99, P = 0.042).(15)

The IMPACT authors sate that *'As ICS use is associated with reduced exacerbation risk, the results from the current analyses coupled with the overall mortality results suggest that the addition of ICS is conferring survival benefits'.*

The 31% reduction the annualised rate of moderate or severe exacerbations for dupilumab in the pooled analysis is greater than the 25% reduction seen in the IMPACT study. From IMPACT the reduction in mortality was 28% so it is not unreasonable to expect a similar or greater mortality benefit for dupilumab treated patients. This suggests that a 'modifier' of some kind should be used alongside the SMRs attributable to current standard care.

Adjusting mortality in the economic model to account for exacerbation benefit

It should be noted that the Whittaker all cause SMRs (by FEV_1 status) used in the model may also underestimate the rate of death in our cohort who have a previous

history of exacerbation because two thirds of the patients included in the Whittaker analysis had no prior exacerbations and the type 2 sub-population in whom risk is expected to be higher, was not analysed. The risk of mortality by exposure group from Whittaker is available and the adjusted HR for the 2 or more exacerbations cohort suggests a 32% increase in mortality risk.

Our choice to include an additional CFR in the model recognised all the above issues but took a simple approach to account for the likely extra mortality benefit due to dupilumab from severe exacerbation reduction.

Several options exist to further modify the mortality calculations in the model:

1. *EAG request to remove the CFR.*

We have described why we believe this is not appropriate above but provide the results in Table 32 below.

Table 32. Scenario 1 deterministic results

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Deterministic							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£49,954
Background Therapy	[redacted]	[redacted]	[redacted]				
Probabilistic							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,884
Background Therapy	[redacted]	[redacted]	[redacted]				

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

2. *Identifying a source for non-exacerbation related COPD mortality and maintaining an excess CFR.*

Several other sources for SMR were identified in the literature and these were provided in sensitivity analysis in the CS. These included Leivseth 2013 and Shavelle 2009.(18, 19) The SMRs for Leivseth are supportive of Whittaker (but collected in Norway not the UK) but the rates in Shavelle are somewhat lower for the very severe health state where most exacerbations are likely to occur (SMR; Shavelle: 2.7 vs Whittaker: 4.1).(14, 19) It is not clear from the publication if the rates in Shavelle include exacerbations or not. No sources were identified which controlled for exacerbations explicitly (but the Whittaker 2023 paper did mention some analyses were adjusted based on exacerbation).

These sensitivity analyses show comparable ICERs to the base case for these alternative sources. Hospitalised severe exacerbations are relatively rare events and implementation of the lower SMR observed in Shavelle confirms that downward adjustment of the SMR in both arms by the same amount is not impactful (Table 33 below).

Table 33. Scenario 2 deterministic results

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Scenario 2 Leivseth							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,810
Background Therapy	[redacted]	[redacted]	[redacted]				
Scenario 2 Shavelle							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,683
Background Therapy	[redacted]	[redacted]	[redacted]				

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

3. *Including only the CFR for severe exacerbation and modelling mortality on age adjusted general population life tables.*

Removal of the excess deaths due to application of the SMR (setting all SMRs to 1 in the model at [Mortality!E33-E36]) and retaining only mortality due severe exacerbation reduces the ICER slightly (Table 34 below) but marginally increases life years and costs as expected because mortality is also associated with lung function decline and other factors.

Table 34. Base case and scenario 3 deterministic results

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Base case							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,408
Background Therapy	[redacted]	[redacted]	[redacted]				

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

This scenario is a more credible option than removing the CFR because it recognises the mortality impact of the differential in severe hospitalised exacerbation events between the two arms. However, it does not account for increased mortality vs. the general population inherent in a progressive lung disease and amongst patients who do not exacerbate.

4. Different SMRs for standard care and dupilumab with no excess CFR.

We spoke to five clinicians about this EAG question, and all were very clear that mortality will be different for dupilumab treated patients because of the proven benefits. A suggestion they made for a scenario was to change the SMR in the dupilumab arm but maintain the SoC SMR if an excess CFR was not appropriate. IMACT was mentioned as the appropriate source.

Therefore, to reflect the expected mortality benefit for dupilumab treated patients vs. standard care using only the SMR (without excess CFR) we have applied an adjustment factor based on IMPACT. As discussed above the hazard ratio for mortality was 0.72 (95% CI, 0.53–0.99, p=0.042) in IMPACT so we have made a simplifying assumption that the full reduction in mortality in moving from triple therapy alone to triple therapy + dupilumab is associated with 28% reduction in the SMRs calculated by Whittaker. This approach was supported by clinical opinion and may be conservative because the reduction in moderate and severe exacerbations observed in IMPACT was smaller than in the pooled BOREAS and NOTUS studies (25% vs 31%). By maintaining an SMR in each arm (in contrast to Scenario 3 above), this methodology may have the benefit of capturing any excess mortality due to the accumulation of moderate exacerbations and cardiovascular events. The adjusted SMRs are shown below (Table 35).

Table 35. Adjustment of SMR by the mortality reduction observed in IMPACT

COPD severity	Whittaker unadjusted (used in the SoC arm)	Whittaker x 0.72 (IMPACT) (used in the dupilumab arm)
Mild COPD	1.000	1.000
Moderate COPD	1.450	1.044
Severe COPD	2.330	1.678
Very Severe COPD	4.100	2.952

The model is not set up to run different SMRs in each arm and we were unable to implement this in the time available for the EAG questions. Therefore, we ran the model twice, with no excess CFR in both runs. Run 1 with the original SMRs from Whittaker to calculate the outcomes for the SOC arm and Run 2 with the adjusted SMRs to calculate the dupilumab outcomes. We then took the SOC and dupilumab outcomes from each run and calculated the ICER from these outside the model. The results are shown overleaf in Table 37. The ICERs derived from the four scenarios above are summarised in Table 36 below.

Table 36. Summary of the scenarios and impact on the base case ICER

Scenario	ICER	Change from base case (%)
Base case	£25,515	N/A
1. EAG requested. Removal of the excess CFR	£49,954	96%
2. Reduction in the SMR to remove exacerbation influence but maintain background mortality due to severity (from Shavelle)	£25,683	1%
3. Removal of all excess mortality (SMR = 1) and only use a CFR	£23,408	-8%
4. Adjustment of SMR for the different arms and remove CFR	£23,210	-9%

Conclusion

Whilst we appreciate that the application of the same SMR in each arm and an additional CFR for exacerbations was a simplifying assumption in our base case this does account for the incremental exacerbation benefit due to dupilumab which we have shown by analogy from the IMPACT study to be very likely to improve mortality outcomes and preserves excess mortality due to COPD severity.

However, to answer this question we have attempted to adjust for any double counting in the application of the same SMR in both arms by exploring some alternative scenarios. Reducing the SMR by using an alternative source to reduce the influence of exacerbations does not move the ICER significantly (1%). Similarly removing any excess mortality at all and modelling only CFR produces a reduction in the ICER of 8%. Perhaps the best alternative to our base case is to remove the excess CFR as requested by the EAG and account for difference in mortality by treating the SMRs in each arm differently. This is Scenario 4 above where the ICER reduces by 9%. Taken together with our base case, these scenarios stress the importance of accounting for expected mortality differences and show broadly

comparable results. They provide confidence that dupilumab remains a cost effective option however mortality might be modelled.

Table 37. Comparison of the ICERS using different SMR

	Dupilumab	Standard care	Dupilumab	Standard care	Dupilumab	Standard care
SMR	**RUN 1: Whittaker (Scenario 1 above)**		**RUN 2: Whittaker x 0.72**		**Combo: Whittaker x 0.72**	**Combo: Whittaker**
QALY outcomes						
QALY - Mild COPD	[redacted]					
No exacerbation	[redacted]					
Moderate exacerbation	[redacted]					
Severe exacerbation	[redacted]					
QALY - Moderate COPD	[redacted]					
No exacerbation	[redacted]					
Moderate exacerbation	[redacted]					
Severe exacerbation	[redacted]					
QALY - Severe COPD	[redacted]					
No exacerbation	[redacted]					
Moderate exacerbation	[redacted]					
Severe exacerbation	[redacted]					
QALY - Very severe COPD	[redacted]					
No exacerbation	[redacted]					
Moderate exacerbation	[redacted]					
Severe exacerbation	[redacted]					
Adverse event utility decrement	[redacted]					
CV event utility decrement	[redacted]					
TOTAL QALYs	[redacted]					
Cost outcomes						
Drug acquisition costs	[redacted]					
Drug administration costs	[redacted]					
Adverse events	[redacted]					
Exacerbation management	[redacted]					
COPD management	[redacted]					

	Dupilumab	Standard care	Dupilumab	Standard care	Dupilumab	Standard care
SMR	**RUN 1: Whittaker (Scenario 1 above)**		**RUN 2: Whittaker x 0.72**		**Combo: Whittaker x 0.72**	**Combo: Whittaker**
CV event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental analysis						
Incremental QALY	[redacted]		[redacted]		[redacted]	
Incremental cost	[redacted]		[redacted]		[redacted]	
ICER	**£49,954**		**£53,011**		**£23,210**	

b) **In addition, the source used to inform the CFR was a meta-analysis of six studies. The EAG notes that none of the studies included in this meta-analysis were UK based and all studies may now be considered relatively out of date (the most recent study included used data collected between 2000-2005 in Norway). Please clarify if any literature searches were undertaken in order to identify more recent studies to inform this parameter?**

A recent UK COPD mortality study, Whittaker et al. 2022,(20) was identified as a source for mortality due to exacerbations. The model gives the user the option to use Whittaker et al. 2022 as the source for excess mortality due to exacerbations, which was included as a scenario analysis.

Additionally, we would like to highlight the 2014 UK National COPD Audit Report, which was previously used in TA461.(21, 22) This report provides a severe exacerbation case fatality rate ranging from 2.1% to 17.8%, depending on the patient's age, and represents a UK-specific data source. The use of the CFR of a flat rate of 15.6% in the model is in line with these UK based estimates. Moreover, the 2023 National Asthma and COPD Audit Programme (NACAP) found that 11.9% of COPD patients died within 90 days after hospitalisation.(23) Similarly, Hartl et al. 2016, a European audit, reported that 10.8% of patients admitted after a severe exacerbation died.(24)

Discontinuation

B23. Priority question: Please clarify if patients who discontinue dupilumab or do not respond to treatment during the 52-week trial period (non-responders) and therefore receive background therapy only from that point forward lose the treatment benefit (in terms of higher FEV_1) associated with dupilumab treatment over background therapy only? In addition, how soon after discontinuation are patients assumed to lose the treatment benefit?

We thank the EAG for the comment. This was implemented in the original model incorrectly, as patients who are non-responders to dupilumab and receive background therapy lose the FEV_1 treatment effect benefit. In other words, patients who are non-responders to dupilumab receive background therapy in the Markov

phase of the model. These patients have a treatment effect duration specific to background therapy (0 years in the base case). The updated model's Markov engine tabs have been modified (cells DQ to GQ) to accommodate this.

B24. Please clarify if the company considered extrapolating clinical trial data on the proportion of patients who discontinued dupilumab using parametric curve fitting? Based on this, please provide the clinical trial data on the proportion of patients who discontinued at each available time point presented as a Kaplan-Meier (KM) curve. Following this, please fit parametric curves to the KM data to extrapolate the data and estimate the long-term discontinuation of patients.

The conduct of clinical trials is designed to ensure that patients remain on treatment as appropriate and that adverse events or other scenarios that may lead to patient led discontinuation in the real world are minimised. Hence, we did not consider extrapolating the discontinuation data from the clinical trials because the protocol driven clinical trial represents a distinctly different environment to the real world in which patients would find themselves once out of the trial setting. It is more informative to consider longer term discontinuation observed in the real world for biologics and dupilumab in particular.

There is no real world experience of dupilumab for the treatment of COPD, but it has been used for several years in patients with asthma and data is available from UK Sanofi homecare in asthma patients. We judged this to be a good proxy to model discontinuation because it is taken directly from dupilumab use in a related respiratory disease and is based in UK patients. The annual discontinuation rate over the first 2 years was ~[redacted]% which was slightly lower than suggested by the expert clinical opinion from our advisory board. The rate in patients with an opportunity to complete 3 years (ie they started 36 months or longer ago and completed year 2) is relatively small so the [redacted] % value is less certain. The data from homecare is provided below.

Table 38. Proportion of patients with asthma discontinuing dupilumab at year 1, 2 and 3.

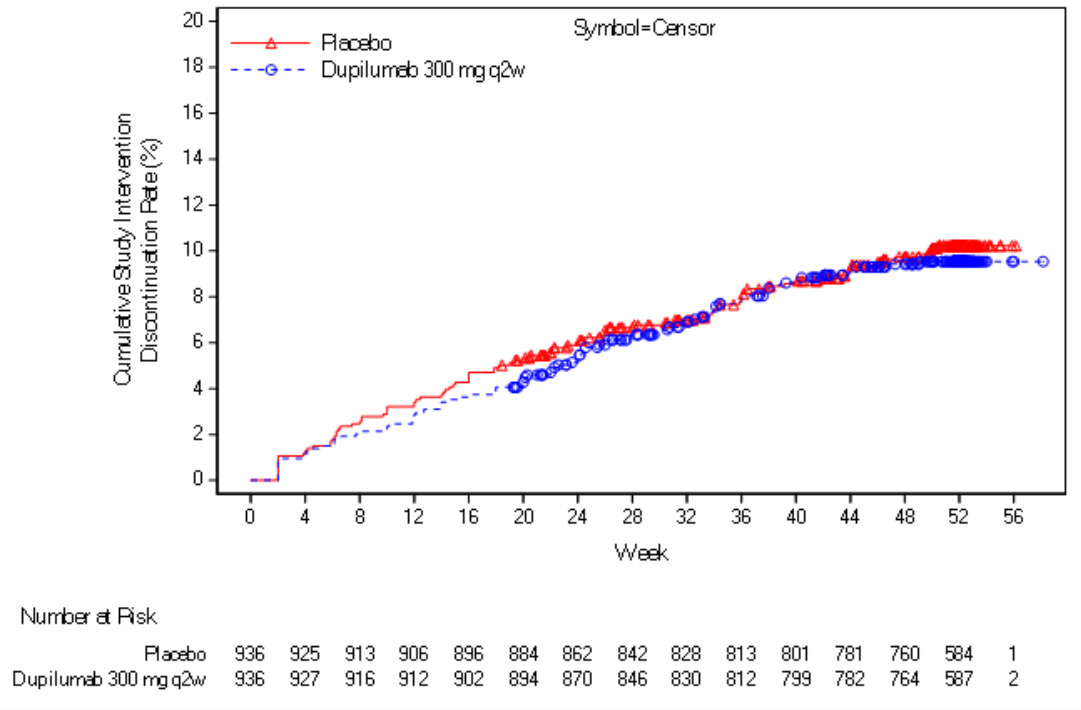
	Year 1	Year 2	Year 3
Total patients with an opportunity to complete the following year	[redacted]	[redacted]	[redacted]
Total patients completing the year	[redacted]	[redacted]	[redacted]
Proportion discontinuing within year	[redacted]	[redacted]	[redacted]

Note that the number finishing year 1 is larger than the number with an opportunity to complete year 2 in the analysis and so on. This is because the number with an opportunity to complete year 2 having completed year 1 is much smaller than the number with an opportunity to compete year 1.

Nonetheless to satisfy the requirements of the EAG question we provide clinical trial data on the proportion of patients who discontinued dupilumab below and use the standard parametric curve fits generally applied in health economic modelling to extrapolate to 10 years.

The Kaplan-Meier plot for time to discontinuation by treatment group in the pooled population is provided below in Figure 7.

Figure 7. Kaplan-Meier plot for time to study intervention discontinuation by treatment group - Pooled ITT population



The fitted data are shown below for the dupilumab treated patients in the pooled ITT population for the Weibull, Log normal, Log logistic and Gamma estimators (Figure 8, Figure 9, Figure 10 and Figure 11).

Figure 8. Weibull fit - Pooled dupilumab ITT population

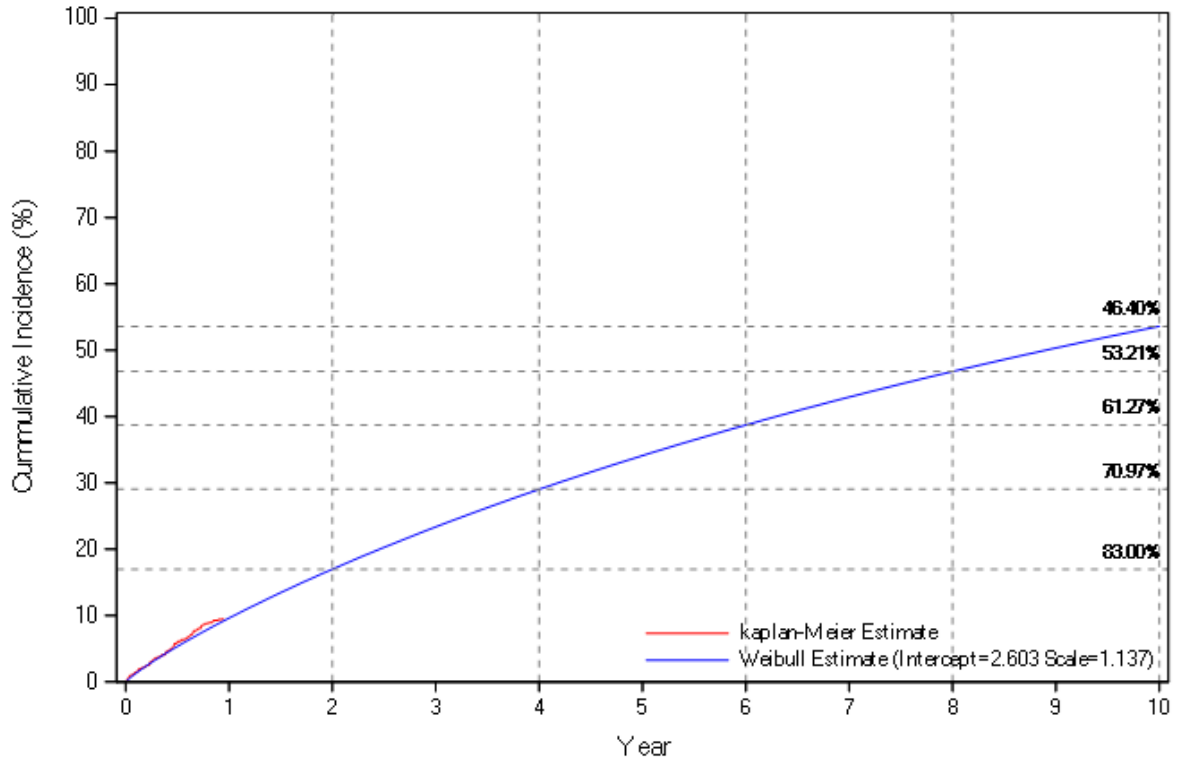


Figure 9. Log normal fit- Pooled dupilumab ITT population

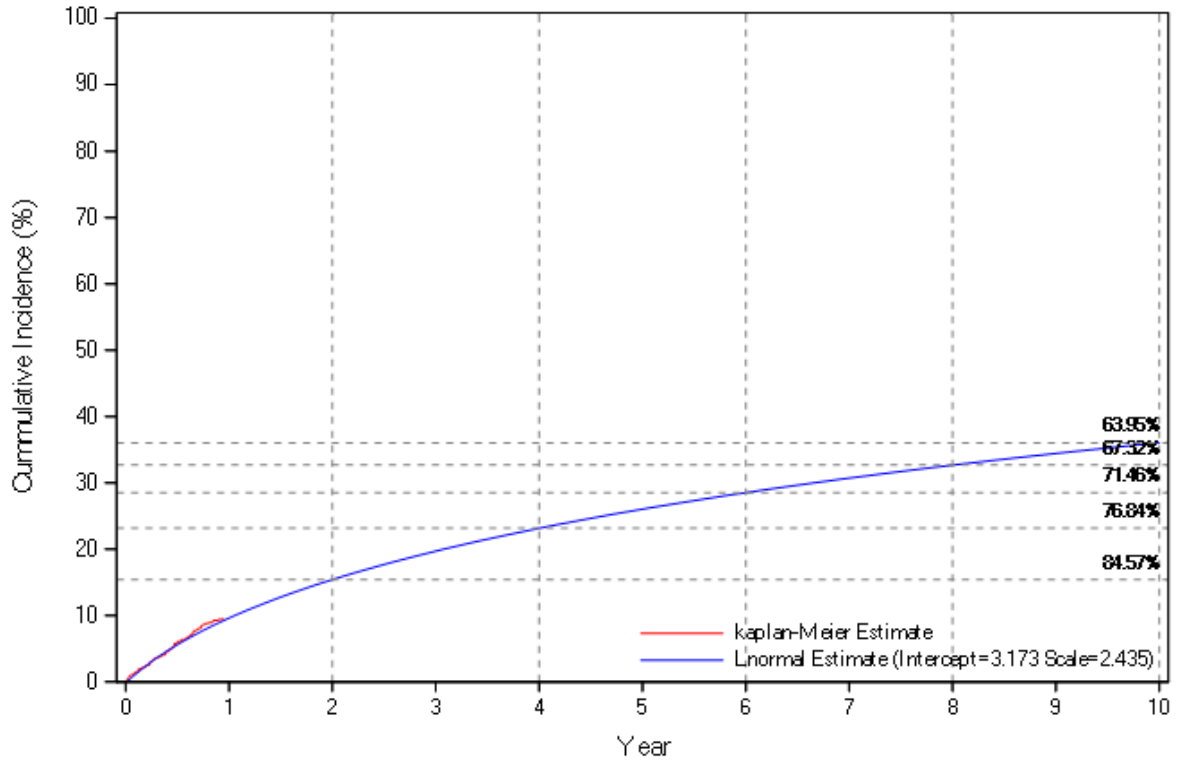


Figure 10. Log logistic fit- Pooled dupilumab ITT population

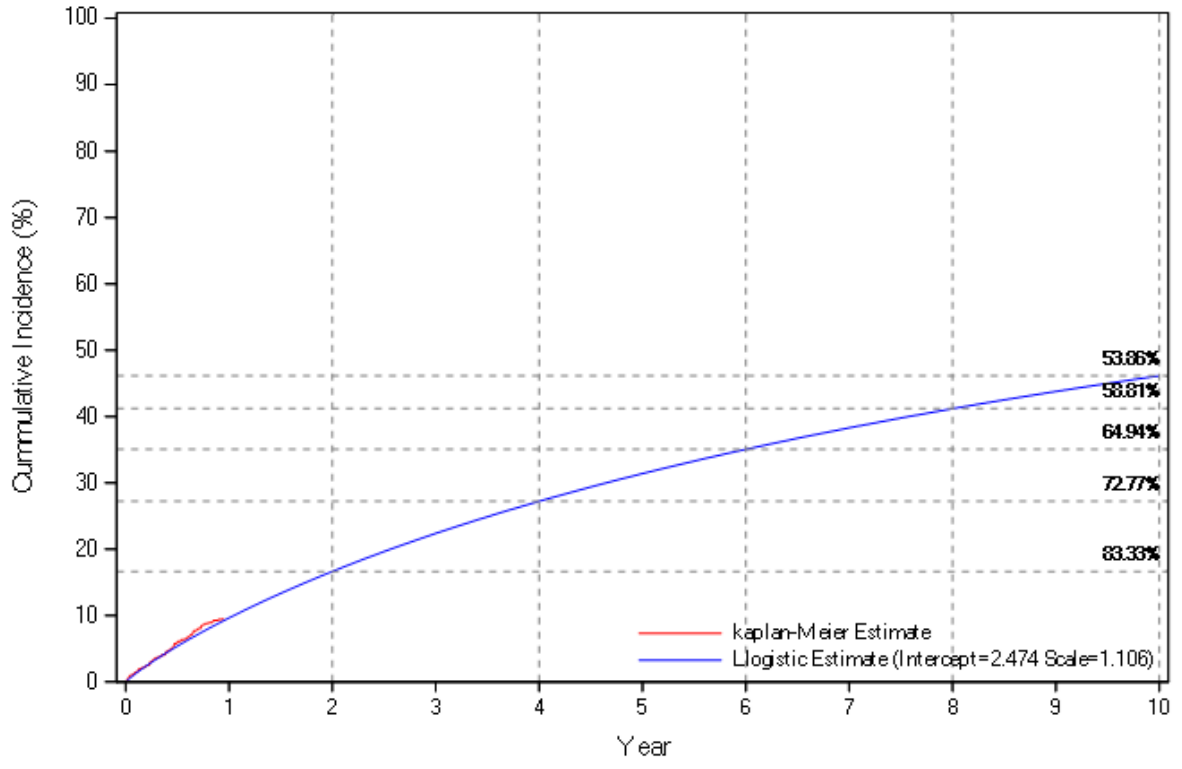
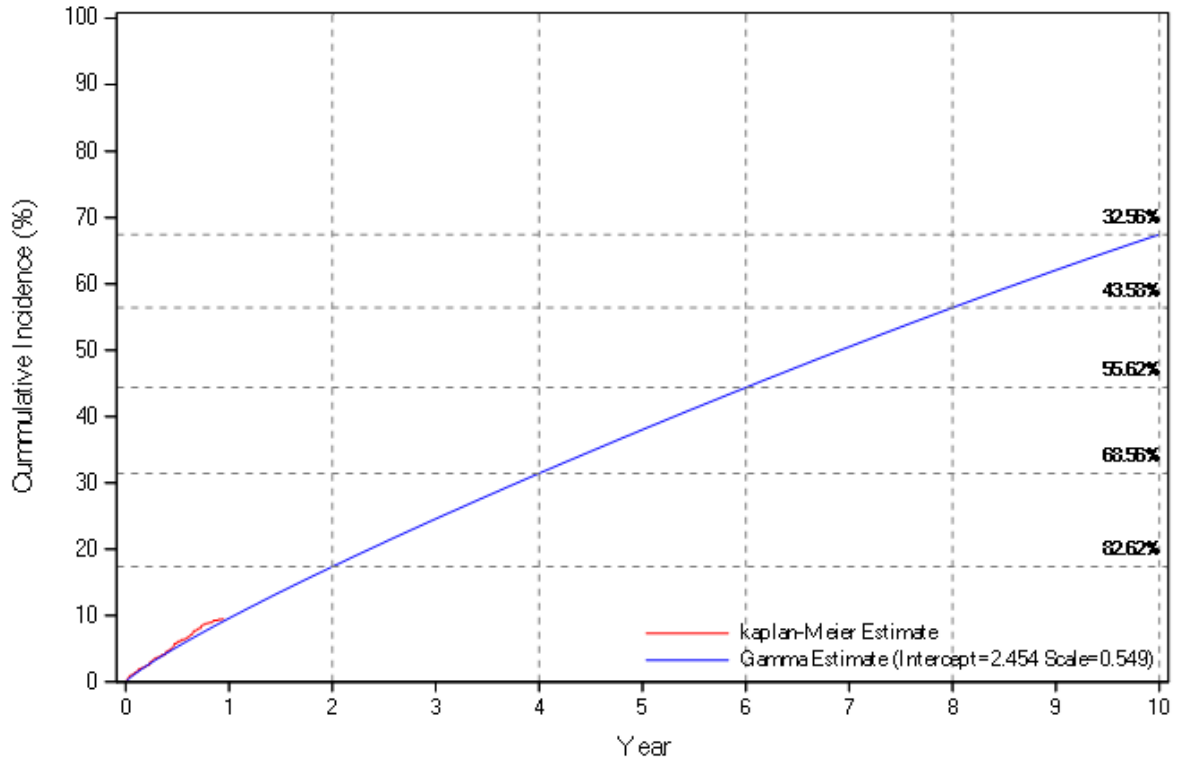


Figure 11. Gamma fit- Pooled dupilumab ITT population



The validation criteria according to fit for the dupilumab population are presented below in Table 39.

Table 39. Validation criteria - Pooled ITT population

Fit	Criterion	Value
Weibull	-2 Log Likelihood	778.071
	AIC (smaller is better)	782.071
	AICC (smaller is better)	782.084
	BIC (smaller is better)	791.754
Log-normal	-2 Log Likelihood	773.903
	AIC (smaller is better)	777.903
	AICC (smaller is better)	777.916
	BIC (smaller is better)	787.586
Log-logistic	-2 Log Likelihood	777.493
	AIC (smaller is better)	781.493
	AICC (smaller is better)	781.506
	BIC (smaller is better)	791.177
Gamma	-2 Log Likelihood	778.691
	AIC (smaller is better)	784.691
	AICC (smaller is better)	784.717
	BIC (smaller is better)	799.216

The AIC, AICC and BIC criteria suggest that the best fit to the data is the Log-normal. This estimate provides the lowest discontinuation rate of the four and is completely at odds with clinical opinion and real-world UK dupilumab experience described above. Fit statistics evaluate only the goodness of fit to the available data and so in this case are unable to accommodate any impact from real world experience. We do not believe any of these estimates are informative.

The 15% real world annual discontinuation rate observed from the homecare data for dupilumab for the treatment of asthma remains the most appropriate source to model long term outcomes.

B25. Based on the proportion of patients reported to complete the 52 week trial period (90.7%), a treatment discontinuation rate of 9.3% is applied as a one-off at 52 weeks. Please confirm if the 9.3% of patients reported to have discontinued includes those who discontinued due to COVID-19. If so, please provide an analysis in which the proportion of patients who discontinue only due to COVID-19 are excluded.

Yes, we confirm that the 9.3% dupilumab arm discontinuation rate in the pooled analysis (87 of 936 randomised and exposed) includes those patients who discontinued due to COVID-19 -related reasons. The rate of discontinuation due to

COVID was 0.75% (7 of 936) and the remaining non-COVID-related discontinuation rate was therefore 8.5%. We have provided a scenario analysis in which the non-COVID-related discontinuation rate during weeks 0-52 of 8.5% has been applied.

Table 40. Cost effectiveness results with a modified rate of 8.5% to account for COVID discontinuation

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Deterministic							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,483
Background Therapy	[redacted]	[redacted]	[redacted]				
Probabilistic							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,827
Background Therapy	[redacted]	[redacted]	[redacted]				

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Arguably COVID-related discontinuations would be considered related to the unique circumstances of the COVID pandemic. However, COVID infection still continues (and is expected to continue) in the real-world post-pandemic. UK clinical expert opinion noted that the pandemic was characterised by an increase in COVID infection but also a drop in infections due to other viruses and bacteria (eg flu), due to social distancing rules, self-isolation and avoidance of non-critical hospital visits. Therefore, in the BOREAS and NOTUS clinical trial settings, it is their view that there should have been a drop in the expected rate of discontinuation for infection types other than COVID. We observed the % of discontinuations in the pooled analysis due to non-COVID-related TEAEs classed as infections and infestations to be very low. For example, just one case of non-COVID-related pneumonia resulted in treatment discontinuation across the two arms of the trial (across 1872 patients). Perhaps low infection-related discontinuations are related to lower total infection rates in BOREAS and NOTUS. We note that the rate of reported (non-COVID) pneumonia in the pooled analysis was between 1.7% (placebo) and 1.3% (dupilumab), whereas in a comparable pre-pandemic population, the ETHOS triple therapy study, reported a pneumonia rate of 4.1% across arms.(25)

Taking these findings into consideration, we do not believe that removing COVID-related discontinuations from the total discontinuation rate would achieve a more valid estimate of a “real” discontinuation rate across the 1st year of treatment with

dupilumab, and that the rate of 9.3% applied in the model is appropriate and should be used without change.

Health-related quality of life

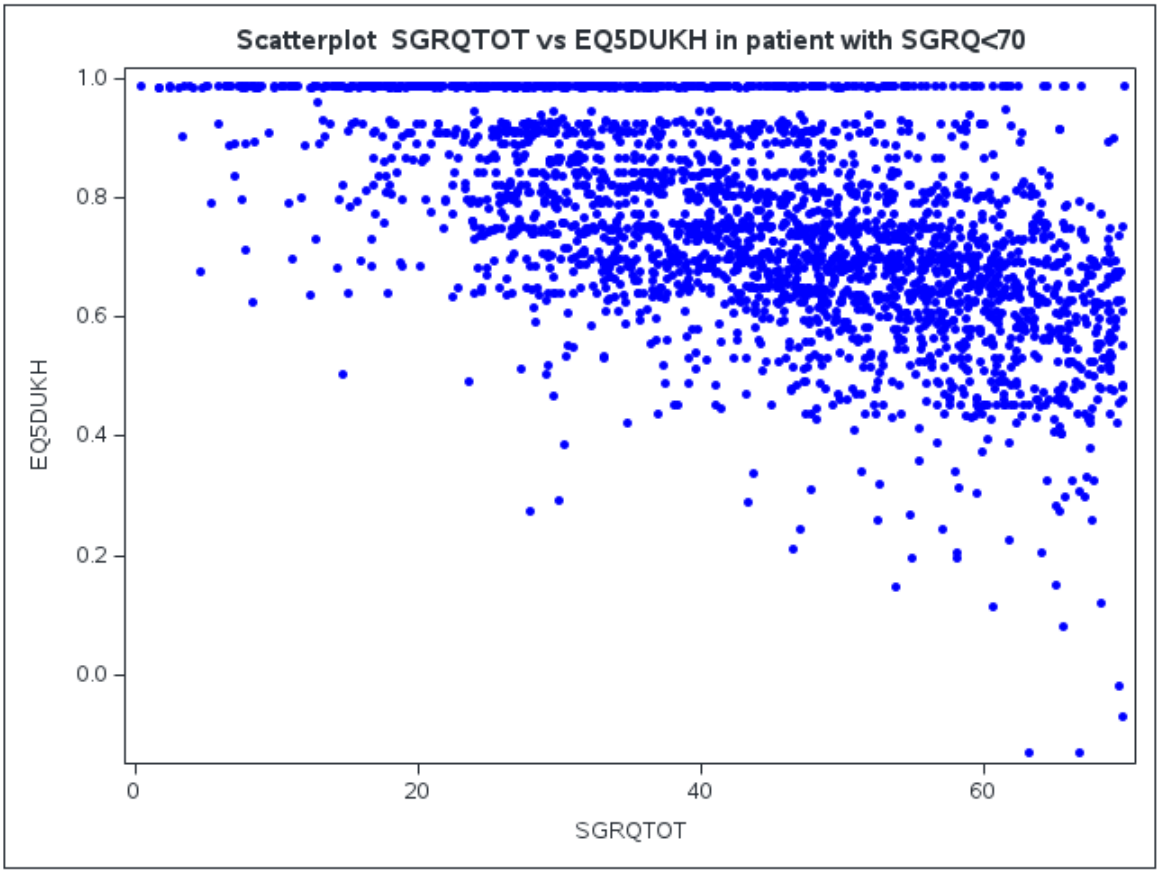
B26. Priority question: Please comment on the validity and strength of the correlation between EQ-5D and SGRQ given that patients with SGRQ scores between 0 and approximately 70 also provided perfect EQ-5D scoring (Figure 27 in the CS). Please also provide the correlation coefficient and significance level with confidence intervals.

Figure 12. Correlation between EQ-5D and SGRQ

Table 41. Pearson correlations between SGRQ total score and EQ-5D-5L UK CW – mapping database

Population	Correlation coefficient	Lower Confidence Limit	Upper Confidence Limit	p-value
All populations	-0.65	-0.67	-0.63	<0.001
SGRQ total score between 1 and 70	-0.57	-0.60	-0.55	<0.001

Figure 13. Scatterplot of EQ-5D-5L index score (Hernandez crosswalk algorithm, UK tariffs) vs SGRQ total score in patients with SGRQ<70 – mapping database.



B27. Priority question: Given that the health state utility differences between dupilumab + background therapy and background therapy alone were not found to be significantly different, please provide further justification for the use of treatment-specific health state utilities. As a scenario, please assume that health state utilities are not treatment-specific.

Firstly, we would like to use this opportunity to clarify a change we made to the model based on the treatment-specific utilities. In the submitted model, the QALYs based on treatment-specific utilities were not calculated correctly. Specifically, the utilities specific to dupilumab + background therapy was applied to patients in the background therapy arm. This has been rectified in the updated model (Refer columns ME to NF in the Markov Engine). All of the results provided in the dossier have been updated and are presented in Appendix 2.

Below is the requested scenario, where non-treatment-specific health state utility values were applied, sourced from Spencer et al 2005 & Sadatsafavi et al 2019 (Table 42).

Table 42. EAG scenario results for question B27

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Deterministic							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,784
Background Therapy	[redacted]	[redacted]	[redacted]				
Probabilistic							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,780
Background Therapy	[redacted]	[redacted]	[redacted]				

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

B28. Priority question: The EAG notes that the pooled ITT utility linear regression (Table 54 in the CS) contains covariates which were not found to be statistically significant. As such, please conduct a scenario analysis using a utility regression rerun to include only statistically significant covariates.

The utility regression was re-run to include only the statistically significant covariates. This is shown below in Table 43.

Table 43. Pooled ITT linear regression of utility based on SGRQ (UK crosswalk tariffs, Hernandez 2020) - Parameter estimates including only statistically significant covariates

Parameter	Estimate (SE)	[95% CI]	p-value
Intercept	[redacted]	[redacted]	<0.0001
SGRQ-based utility at baseline	[redacted]	[redacted]	<0.0001
Health State - severity of airflow obstruction			
Moderate FEV_1	[redacted]	[redacted]	<0.0001
Severe FEV_1	[redacted]	[redacted]	<0.0001
Very Severe FEV_1	[redacted]	[redacted]	<0.0001
Health State - exacerbation risk			
Moderate	[redacted]	[redacted]	<0.0001
Severe	[redacted]	[redacted]	<0.0001

CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; mg = milligrams; P-value = Probability value for the T Statistic; q2w = administered every two weeks; SE = standard error; SGRQ = St. George's Respiratory Questionnaire; UK = United Kingdom

The LS mean utilities by health state calculated from the utility regression above without statistically significant covariates are provided below in Table 44.

Table 44. Pooled ITT linear regression of utility based on SGRQ (UK crosswalk tariffs, Hernandez 2020) – LS means by health state

Health state	LS Mean (SE)	[95% CI]	p-value
Mild FEV_1	[redacted]	[redacted]	<0.0001
Moderate FEV_1	[redacted]	[redacted]	<0.0001
Severe FEV_1	[redacted]	[redacted]	<0.0001
Very Severe FEV_1	[redacted]	[redacted]	<0.0001
Exacerbations			
No exacerbation	[redacted]	[redacted]	<0.0001
Moderate exacerbation	[redacted]	[redacted]	<0.0001
Severe exacerbation	[redacted]	[redacted]	<0.0001

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; ITT = intent-to-treat; LS = least squares; SGRQ = St. George's Respiratory Questionnaire; UK = United Kingdom

The cost effectiveness results including the utility estimates from Table 44 are provided below in Table 45.

Table 45. EAG scenario results for question B28

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Deterministic ICER							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,237
Background Therapy	[redacted]	[redacted]	[redacted]				
Probabilistic ICER							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,179
Background Therapy	[redacted]	[redacted]	[redacted]				

B29. The EAG was unable to validate the company's preferred CV event disutilities (Sterne et al. 2017) as the values reported by Sterne are sourced from Robinson et al. 2001. Please provide a reference for Robinson et al. 2001, if this is not possible, please conduct a scenario analysis using CV event utilities from Ara and Brazier, 2010 or an alternatively appropriate source.

CV event utilities from Ara and Brazier, 2010 has been incorporated into the updated model as a scenario.

Table 46. EAG scenario results for question B29

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Deterministic ICER							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,232
Background Therapy	[redacted]	[redacted]	[redacted]				
Probabilistic ICER							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,323
Background Therapy	[redacted]	[redacted]	[redacted]				

B30. The EAG notes that the SLR conducted by the company only included one study which measured EQ-5D values within the context of COPD (Jacket *et al.* 2024 [ETHOS trial]). Please can the company therefore provide a reasoning as to how the SLR did not capture the additional studies used by the company to provide alternative health state utility scenarios (Spencer *et al.* 2005, Sadatsafavi *et al.* 2019, Rutten Van Molken *et al.* 2006, Borg *et al.* 2004)?

The SLR conducted by the company was designed to supplement the evidence base from NICE Guideline 115 (NG115)(26) by restricting the search to studies published from 1 January 2017 onward. This approach ensured the inclusion of recent and relevant data while building upon the comprehensive evidence previously evaluated in NG115.

As a result, earlier studies, such as Spencer 2005(27), Rutten van Molken 2006(28), and Borg 2004(29), were not identified in the SLR as they fall outside of the defined search period.

The study by Sadatsafavi 2019(30) was identified during the SLR but excluded during screening as it did not report primary data. Instead, it derived utility values from the published literature, with the primary sources also being outside of the SLR search period.

As highlighted in the submission, none of the studies identified by the SLR reported UK-specific utility values for each COPD state. Therefore, it was necessary to consider evidence published prior to the SLR cut-off date. Specifically:

- Rutten van Molken 2006 was included as it is the source of the utility scores by GOLD stage used in the NICE NG115 model report and the roflumilast technology appraisal guidance.
- Spencer 2005 and Borg 2004 were identified through a targeted review of prior COPD models, which frequently cited these studies for health state utility values.

B31. In the scenario which includes the chronic impact of exacerbations, the assumed disutility has been derived from Rutten van Molken *et al.* The EAG notes that HRQoL was captured in this study using vignettes opposed to EQ-5D data as preferred in the NICE guidance. As such, please conduct a scenario exploring the chronic disutility associated with exacerbations using Jacket *et al.* 2024 (table below) or an alternative appropriate source.

Exacerbation	Disutility
Moderate	0.014 (CI: 0.011, 0.016)
Severe	moderate disutility + 0.011 (CI: 0.003, 0.018)

To clarify, the model's base case uses exacerbation disutilities derived from the pooled ITT SGRQ to EQ-5D-3L mapping exercise (Document B, Table 59). The exacerbation disutility values from Rutten van Molken et al., which are also used in the NICE NG115 COPD economic model, were only utilised in the scenario analysis with published health state utility values.

Table 47. EAG scenario results for question B31

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Deterministic ICER							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,074
Background Therapy	[redacted]	[redacted]	[redacted]				
Probabilistic ICER							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,408
Background Therapy	[redacted]	[redacted]	[redacted]				

Costs and resource use

B32. Priority question: Clinical expert advice provided to the EAG suggests that 100% of patients would not be able to self-administer dupilumab due to age, frailty or other complicating factors and that approximately 5% may need professional assistance. Therefore, please conduct a scenario assuming 5% of patients require support with dupilumab administration.

Table 48. EAG scenario results for question B32

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Deterministic ICER							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,680
Background Therapy	[redacted]	[redacted]	[redacted]				
Probabilistic ICER							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,796
Background Therapy	[redacted]	[redacted]	[redacted]				

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Updated B33. Priority question: The EAG's clinical experts additionally stated while trialling patients on dupilumab, full blood monitoring would be conducted on a three-monthly basis during the trial period. Please explore a scenario in which dupilumab patients receive full blood analysis every three months for the first year of treatment.

Thank you for your clarification and for updating the question. However, we maintain that the proposed frequency of blood monitoring is excessive. The BOREAS and NOTUS studies did not identify significant disturbances occurring in patients treated with dupilumab, and therefore there are no requirements for blood monitoring specified in the SmPC for dupilumab. Furthermore, we have consulted with UK clinical experts experienced in prescribing dupilumab for asthma and/or likely to prescribe dupilumab for COPD in the future, and they confirmed that in their clinical practice, they do not/would not request full blood counts every three months to monitor dupilumab during the first year of treatment. Respondents mostly stated that blood counts were not asked for at all in the absence of a clinical rationale or symptoms, whilst a few stated that in severe asthma they only routinely monitor at annual or bi-annual patient review, as the results rarely influence treatment decisions. It was also noted that excessively frequent monitoring of blood counts

would be an unnecessary burden on COPD patients, especially for those with (common) mobility issues.

Table 49. EAG scenario results for question B33

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Deterministic ICER							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,553
Background Therapy	[redacted]	[redacted]	[redacted]				
Probabilistic ICER							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,732
Background Therapy	[redacted]	[redacted]	[redacted]				

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

B34. Priority question: The EAG's clinical experts noted that the company's assumptions about the frequency of spirometry tests were optimistic. In their view, in current clinical practice mild and moderate patients would be unlikely to receive spirometry and severe and very severe COPD patients may receive spirometry once annually. Please conduct a scenario assuming these frequencies.

Please refer to the updated model, which includes a scenario reflecting the spirometry frequency assumptions provided by the EAG's clinical experts. It should also be noted that the spirometry frequencies used in the original base-case model were derived from the NICE COPD Guidelines model report. These frequencies were based on the opinions of NICE committee members and were intended to reflect clinical practice.

Table 50. EAG scenario results for question B34

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Deterministic							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,478
Background Therapy	[redacted]	[redacted]	[redacted]				
Probabilistic							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,689
Background Therapy	[redacted]	[redacted]	[redacted]				

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

B35. When asked to validate the health care resources and frequencies assumed in the model, the EAG's clinical experts noted that after experiencing a severe

exacerbation COPD patients would be treated with steroids and antibiotics, as has been assumed for moderate exacerbations but not for severe exacerbations. Has the company excluded these costs by implicitly assuming that these costs would be included in the hospital stay? If not, what was the reasoning for not including these resources?

Yes, we assumed that the costs for antibiotics and oral corticosteroids would be included in the hospital stay costs. This simplification was made to avoid double counting.

B36. Please can the company clarify if the 18% of patients followed-up within 30 days of an exacerbation in Table 66 of the CS are part of the same 37% of patients assumed to be followed up by 90 days or are they different? If part of the same, please conduct a scenario assuming only 37% of patients are followed up.

Yes, the 18% who were followed up within 30 days are included within the 37% who were followed up after 90 days. Therefore, the 37% scenario will be implemented.

Table 51 EAG scenario results for question B36

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Deterministic							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,543
Background Therapy	[redacted]	[redacted]	[redacted]				
Probabilistic							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,753
Background Therapy	[redacted]	[redacted]	[redacted]				

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

B37. Please can the company confirm if the assumption of one day in hospital following a severe exacerbation is correct (Table 66 in the CS), given 2.9 days was identified in the company's resource use analysis (Table 1 in Appendix M).

We apologise for the confusion. The hospital stay is implemented in the model as an episode attracting the cost shown in Table 66 in the CS. It is not calculated by applying a daily rate to the number of days spent as an inpatient.

B38. Table 1 in Appendix M states that ICU days is 0.01 whereas Table 66 in the CS reports 1% having ICU stay. Please clarify this difference and make any necessary amendments.

The HES severe exacerbation study reported that there were 8,135 ICU days which averages 0.01 ICU days per severe exacerbation.

B39. Please comment on the appropriateness of including CPAP in the model following a severe exacerbation given ventilation is already included.

We identified both CPAP and ventilation procedures occurring following severe exacerbation in our analysis of the HES data. These are coded separately in HES as CPAP and ventilation are different procedures - with CPAP applying a constant pressure to open airways and increase lung volume, whereas ventilation applies two levels of pressure to move air in and out of the lungs. To capture a full picture of activity and costs relating to severe exacerbations both were provided as model inputs.

B40. Please provide the NHS cost codes used for the weighted resource use costs reported in the CS.

Please find document “COPD NHS reference unit cost” embedded.

COPD NHS reference unit costs.xlsx

B41. The final NICE scope states that the comparator includes “*Standard care without dupilumab (triple inhaled therapy or double therapy where ICS is not appropriate)*”. Please clarify why in the economic model, the basket of therapies for standard care consists of triple therapies only (ICS/LABA/LAMA), with 0% assumed to receive double therapy (LABA/LAMA)?

In our HTA advisory board, we consulted clinical experts to estimate the proportion of patients on dual therapy who are contraindicated to inhaled corticosteroids. The consensus among the experts was that such cases are exceedingly rare, with the number of affected patients being described as "almost none." Consequently, to simplify the background therapy arm, we included only triple therapy and excluded dual therapy.

26/11/2024 Additional clarification questions (ACQs)

ACQ1. Priority question.

The CS states that data on CV events following exacerbations were derived from post-hoc analysis of the large international SUMMIT RCT, in lieu of relevant UK data. However, the EAG identified the following study which provides data on non-fatal CVD events following exacerbations, based on patients with COPD in England.(31) The EAG considers this to be an appropriate source of England-specific data. Therefore, please update the company base case to use data from this study or include it as a scenario analysis. Specifically, data from Supplementary material, Appendix E2. Table E2.1. Risk of composite cardiovascular event during follow-up, comparing patients by index exacerbation (A: dichotomised; B; by severity).

Due to the timing of these questions, we have had to prioritise addressing other queries to ensure high-quality responses across the main body of questions. Given that cardiovascular (CV) events have a minimal impact on the ICER, they were not a primary focus in our analysis.

To provide clarity, we have included a scenario below where all CV events are removed from the model by toggling the switch at Cell L40 on the [General inputs] worksheet. The results demonstrate that CV events have a negligible impact on the ICER, supporting our decision to prioritise other questions.

Table 52. CV event removal scenario analysis results

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Deterministic							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,638
Background Therapy	[redacted]	[redacted]	[redacted]				
Probabilistic							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,866
Background Therapy	[redacted]	[redacted]	[redacted]				

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

ACQ2.

In the footnote of Table 68 outlining the incidence of CV events, HR is stated to stand for hazard ratio. However, the calculations performed by the company appear to refer to a hazard rate. Please clarify if this was a typo and should instead state

hazard rate?
We thank the EAG for the comment. In the footnote of Table 68, HR stands for hazard rate.

ACQ3.
Footnote of Table 68 states that the probabilities were derived from transforming the hazards to an annual probability. The EAG was unable to replicate the annual probabilities in Table 68 obtained by the company. Please clarify the exact calculations and numbers used to inform each probability of CV events associated with each exacerbation state and provide a step-by step worked example.
We have excluded CV events in our response to ACQ1 and have shown this has very little impact on the ICER. Unfortunately, we were not able to answer this question within the time frame of the response but given this is not a priority question we hope we can follow up later with the worked example.

ACQ4.
Kunisaki et al. 2018 presented data on CV events for all exacerbations and those requiring hospitalisation, used to represent severe exacerbations. The data for all exacerbations includes those patients who required hospitalisation (i.e. severe exacerbation). Please clarify if the company used data on all exacerbations to represent moderate exacerbations as opposed to subtracting the hospitalisations from all exacerbations?
Please refer to our response for question ACQ1 which demonstrates a scenario which excluded the effect of CV events. We thank the EAG for the comment.

ACQ5.
The CS states that data from Kunisaki et al. was adjusted to include non-fatal CV events only. Please clarify how these adjustments were made.
Please refer to our response for question ACQ1.

ACQ6.
Please provide the results from the pooled analysis for the following E-RS subgroups from the EXACT tool (as provided for Change from baseline in E-RS: COPD total score on page 85, Document B):

RS-Breathlessness

RS-Cough and Sputum

RS-Chest Symptoms

Table 53. E-RS: COPD RS – Subgroups

Week 52	Placebo (N=830)	Dupilumab (N=830)
Number of patients remaining in the study	[redacted]	[redacted]
Change (SD) from baseline in E-RS: COPD RS-Breathlessness up to week 52 visit	[redacted]	[redacted]
Change (SD) from baseline in E-RS: COPD RS-Cough and Sputum up to week 52 visit	[redacted]	[redacted]
Change (SD) from baseline in E-RS: COPD RS-Chest Symptoms up to week 52 visit	[redacted]	[redacted]

ACQ7.

Section B.3.3.4 of the CS states "The proportions of patients experiencing different numbers of exacerbation events is taken from the 52-week study period according to the pooled analysis", shown in Table 44. However, the economic model appears to apply the proportion of patients experiencing exacerbations based on the year prior to trial randomisation. Please clarify the data used in the model base-case and provide an updated table of the proportions used in the economic base-case. In addition, the trial data shown in Table 44 corresponds with inputs in the "dupilumab trial inputs" sheet for 'all patients' and 'background therapy'. However, the data for responders differs to that used in the model in cells M457:M462. Please clarify if the data in the table or the economic model is correct?

To mitigate the expected low exacerbation rates observed in clinical trials compared with the real world while keeping as closely as possible to the trial population data, we have used patient data (placebo and dupilumab combined) from the year prior to randomisation as the baseline exacerbation rate in the base case. However, ‘the proportions of patients experiencing different numbers of exacerbation events’ were informed by the 52-week study period, assuming they are applicable to different baseline exacerbation rates.

The data for responders used in the model in cells M457:M462 are correct. The numbers shown in Table 44 in the report are incorrect and should be updated to align with the model inputs.

Appendix 1. Updates made to the original model based on EAG comments

Eliminating the results macro and creating treatment specific Markov engines

One of the EAG comment was to eliminate the macro that was used in the original model which necessitated the results to be rerun at every instance of a parameter change. This was noted and we have eliminated the deterministic results macro and created 7 Markov engines that are treatment specific. This ensures that the deterministic results are instantly populated.

First cycle of the Markov Engine

In question B6. In the 'Markov_engine' model sheet, the first row (row 35) is said to correspond to the distribution at the end of the trial period. However, the age is set to 65. If patients are 65 at the beginning of the trial then by the end of the decision tree period (52 weeks) they should be 66. Please clarify if this is correct and amend the model as necessary., the EAG pointed out that the age corresponding to the first cycle of the Markov engine is incorrect. Since the first cycle corresponds to the distribution at the end of the trial period and the starting age has been set to 66 (1 year after the trial start) instead of 65 from the original model. The changes made ensures the following:

- Starting age of patients in the Markov engine is 66 (cell I35)
- General population utility of patients in the first cycle of Markov corresponds to patients who are 66 years old (cell ME35)

In question B7. Discounting should not be implemented in the first year of the model; however, in the 'Markov_engine' model sheet, discounting is being applied for costs and utilities (columns F and G) from the model cycle corresponding to the trial period (baseline to 52 weeks). Please amend this error in the model so that discounting is only applied from year 1 onwards., it was highlighted by the EAG to not implement discounting in the first year of the Markov model. However, we have clarified that while it is the first cycle of the Markov, it is the first year of the modelled population and hence discounting must be implemented. However, the formulae in columns F and G in the latest model has been updated to reflect the discounting corresponding to the first year of the modelled population. Question B8. Please clarify why in cell

H35 of ‘Markov_engine’, time in weeks at end of cycle is 0 whereas time in years at end of cycle (cell I35) is 1? If this is an error, please amend the model. by the EAG asked for the clarification on the ‘time in weeks at the end of cycle column’ (H35) in the original model. Since this did not have any dependencies, and was causing confusion to interpret the trace, we have removed the column. We hope the Markov engines in the updated model with the changes made clarify the EAG’s concern on the first cycle of the Markov engine, with the appropriate age, and discounting applied.

Treatment specific utility calculation

In the submitted model, the QALYs based on treatment-specific utilities (which was the base case) were not calculated correctly. The Markov trace is constructed in a way that the discontinuers/non-responders to add-on dupilumab treatment is split from the continuers/responders. The COPD-stage utility of dupilumab was applied to the latter whereas the COPD-stage utility of background therapy was applied to the former. This works for all add-on treatments except background therapy (idx=2) which has no discontinuers/non-responders by definition. The original model was applying the COPD-stage utility of dupilumab to patients on background therapy. This has been rectified in the updated model. (Refer columns ME to NF in the Markov Engine)

FEV_1 Treatment Effect Duration on Non-responders

The EAG asked on the FEV1 treatment effect duration of patients who discontinue dupilumab or do not respond to dupilumab in *B23. Priority question: Please clarify if patients who discontinue dupilumab or do not respond to treatment during the 52-week trial period (non-responders) and therefore receive background therapy only from that point forward lose the treatment benefit (in terms of higher FEV1) associated with dupilumab treatment over background therapy only? In addition, how soon after discontinuation are patients assumed to lose the treatment benefit? T*he original base case assumes that the FEV1 treatment effect of patients who receive dupilumab (and responded) last for 2 years. In other words, patients who were non-responders to dupilumab and started with background therapy in the first cycle of Markov engine should have the FEV1 treatment effect duration of 0 years. However, this was not implemented correctly in the originally submitted model as it assumed

that non-responders to dupilumab who receive background therapy still have a treatment effect of 2-years post trial period. This has been rectified in the latest model by updating the trace of discontinuers/non-responders (cells DQ to GQ) in the latest model engine to ensure that the FEV_1 treatment effect duration of non-responders is correctly applied.

CV Event Incidence in the trial period

The CV event incidence of the two arms in the trial period has been updated to reflect the non-fatal CV events in the model.

Other updates specific for PSA

In order to accurately run the PSA, the number of patients at trial start for dupilumab and background therapy is used to calculate uncertainty estimates instead of using a naïve assumption of the SE being 20% of the mean value. This is specifically used for proportion of responders, proportion of patients at amelioration and maintenance phases, and discontinuation rates. In addition, the CI for the SMR due to excess mortality due to exacerbation from Whittaker 2022 has been incorporated in the latest model for better uncertainty estimates.

Proportion of patients by COPD stage at trial start

We identified a minor issue with the % of patients by COPD stage at trial start for both treatment arms in the original model. We have updated this in the rectified model. Please refer the below table that reflects the updates made. Since the % at the end of amelioration and maintenance are correct, this has a minor effect on the results of the model. We apologise for the error which was caused by an oversight on our part.

COPD Stage	**ITT**	**FeNo >=20**	**EOS>=500**
Mild COPD	2.4%	3.2%	2.3%
Moderate COPD	47.0%	50.1%	49.6%
Severe COPD	47.7%	44.8%	45.8%
Very severe COPD	3.0%	2.0%	2.3%
Updated model			
Mild COPD	1.9%	2.6%	2.0%
Moderate COPD	47.9%	50.7%	48.9%
Severe COPD	47.6%	45.0%	47.1%
Very severe COPD	2.5%	1.7%	2.0%

Appendix 2: Updated results from the original CS

The following tables are numbered to correspond to the tables in the original CS.

Corresponding to B.3.10 in the CS. Base case results

Table 54. Corresponding to Table 77 in the CS. Base case deterministic results

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,515
Background Therapy	[redacted]	[redacted]	[redacted]				

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Table 55. Corresponding to Table 78 in the CS. Summary of PSA results

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,624
Background Therapy	[redacted]	[redacted]	[redacted]				

CI = confidence interval; ICER = incremental cost-effectiveness ratio; LY = life year; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Corresponding to Appendix J. Clinical outcomes from the model

Table 56. Corresponding to Table 1 in Appendix J. Summary of dupilumab model results compared with incidence rates from the pooled BOREAS and NOTUS trials

	Dupilumab + Background Therapy		Background Therapy	
Outcome	Clinical trial result	Model result[a]	Clinical trial result	Model result[a]
Number of exacerbations[b]	0.63	[redacted]	0.89	[redacted]
Moderate exacerbation[b]	0.59	[redacted]	0.81	[redacted]
Severe exacerbation[b]	0.05	[redacted]	0.08	[redacted]
Number of deaths	0.02	[redacted]	0.02	[redacted]
Non-fatal CV events	0.01	[redacted]	0.02	[redacted]

CV = cardiovascular

[a]The model results are derived from the initial year (decision tree) of the trial period.

[b]Pooled ITT unadjusted annualised exacerbation event rate.

Disaggregated results of the base-case incremental cost-effectiveness analysis

Table 57. Corresponding to Table 2 in Appendix J. Summary of disaggregated results (LYs)

Outcomes	Dupilumab + Background Therapy	Background Therapy
LYs - Mild COPD	[redacted]	[redacted]
No exacerbation	[redacted]	[redacted]
Moderate exacerbation	[redacted]	[redacted]
Severe exacerbation	[redacted]	[redacted]
LYs - Moderate COPD	[redacted]	[redacted]
No exacerbation	[redacted]	[redacted]
Moderate exacerbation	[redacted]	[redacted]
Severe exacerbation	[redacted]	[redacted]
LYs - Severe COPD	[redacted]	[redacted]
No exacerbation	[redacted]	[redacted]
Moderate exacerbation	[redacted]	[redacted]
Severe exacerbation	[redacted]	[redacted]
LYs - Very severe COPD	[redacted]	[redacted]
No exacerbation	[redacted]	[redacted]
Moderate exacerbation	[redacted]	[redacted]
Severe exacerbation	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]

COPD = chronic obstructive pulmonary disease; LY = life year

Table 58. Corresponding to Table 3 in Appendix J. Summary of disaggregated results (QALYs)

Outcomes	Dupilumab + Background Therapy	Background Therapy
QALYs - Mild COPD	[redacted]	[redacted]
No exacerbation	[redacted]	[redacted]
Moderate exacerbation	[redacted]	[redacted]
Severe exacerbation	[redacted]	[redacted]
QALYs - Moderate COPD	[redacted]	[redacted]
No exacerbation	[redacted]	[redacted]
Moderate exacerbation	[redacted]	[redacted]
Severe exacerbation	[redacted]	[redacted]
QALYs - Severe COPD	[redacted]	[redacted]
No exacerbation	[redacted]	[redacted]
Moderate exacerbation	[redacted]	[redacted]
Severe exacerbation	[redacted]	[redacted]
QALYs - Very severe COPD	[redacted]	[redacted]

Outcomes	Dupilumab + Background Therapy	Background Therapy
No exacerbation	[redacted]	[redacted]
Moderate exacerbation	[redacted]	[redacted]
Severe exacerbation	[redacted]	[redacted]
CV event utility decrement	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]

COPD = chronic obstructive pulmonary disease; QALY = quality-adjusted life year

Table 59. Corresponding to Table 4 in Appendix J. Summary of disaggregated results (costs)

Outcomes	Dupilumab + Background Therapy	Background Therapy
Drug acquisition costs	[redacted]	[redacted]
Drug administration costs	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]
Exacerbation management	[redacted]	[redacted]
COPD management	[redacted]	[redacted]
CV event costs	[redacted]	[redacted]
Total costs	[redacted]	[redacted]

COPD = chronic obstructive pulmonary disease; CV = cardiovascular

Table 60. Corresponding to Table 5 in Appendix J. Summary of disaggregated results (health outcomes)

Outcomes	Dupilumab + Background Therapy	Background Therapy
Number of exacerbations	[redacted]	[redacted]
Moderate exacerbation	[redacted]	[redacted]
Severe exacerbation	[redacted]	[redacted]
Number of deaths	[redacted]	[redacted]
Deaths in mild COPD	[redacted]	[redacted]
Deaths in moderate COPD	[redacted]	[redacted]
Deaths in severe COPD	[redacted]	[redacted]
Deaths in very severe COPD	[redacted]	[redacted]
Deaths in no exacerbation	[redacted]	[redacted]
Deaths in moderate exacerbation	[redacted]	[redacted]
Deaths in severe exacerbation	[redacted]	[redacted]
Number of responders	[redacted]	[redacted]
CVD associated outcomes	[redacted]	[redacted]
Time on treatment (years)	[redacted]	[redacted]
Time off treatment (years)	[redacted]	[redacted]

COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease

Corresponding to B.3.11 in CS. Exploring uncertainty

Probabilistic sensitivity analysis

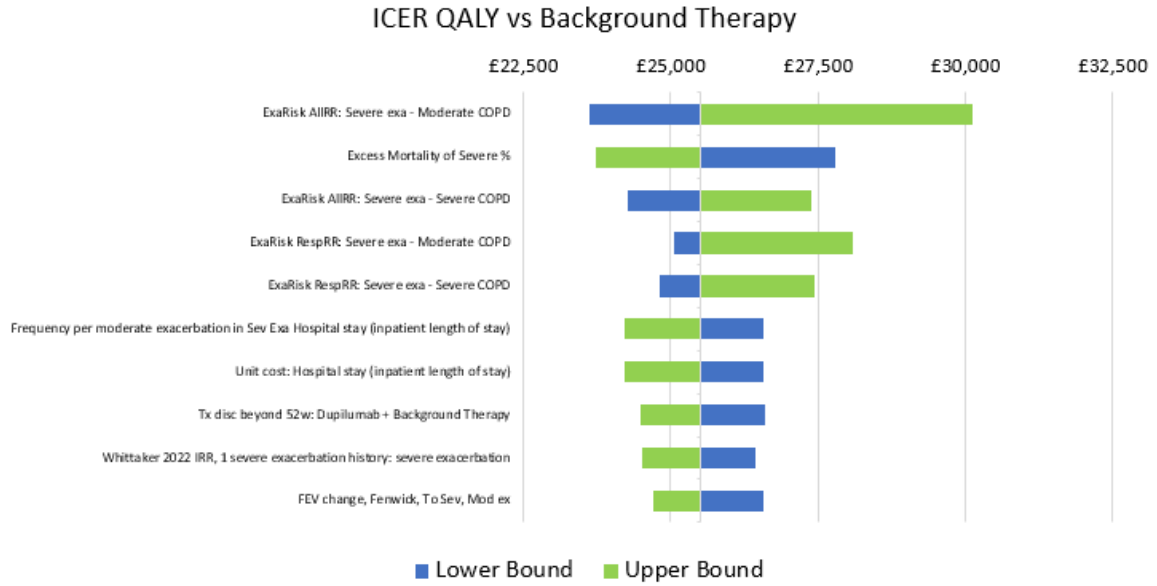
Figure 14. Corresponding to Figure 31 in the CS. Scatter plot for incremental cost-effectiveness results (1,000 iterations)

PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 15. Corresponding to Figure 32 in the CS. Cost-effectiveness acceptability curve (1,000 iterations

Deterministic sensitivity analysis

Figure 16. Corresponding to Figure 33 in the CS. Tornado diagram of ICER (incremental cost per QALY gained) of dupilumab + background therapy vs. background therapy



COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; ICER = incremental cost-effectiveness ratio; IRR = incidence rate ratio; QALY = quality-adjusted life year; Tx = treatment; w = weeks

Table 61. Corresponding to Table 79 in the CS. Top 10 drivers of the ICER results

Rank	Parameter	ICER - Lower Bound	ICER - Upper Bound	Difference
Base case ICER				
1	ExaRisk AllRR: Severe exa - Moderate COPD	£23,629	£30,132	£6,503
2	Excess Mortality of Severe %	£27,792	£23,718	£4,074
3	ExaRisk AllRR: Severe exa - Severe COPD	£24,280	£27,382	£3,102
4	ExaRisk RespRR: Severe exa - Moderate COPD	£25,058	£28,094	£3,036
5	ExaRisk RespRR: Severe exa - Severe COPD	£24,809	£27,430	£2,621
6	Frequency per moderate exacerbation in Sev Exa Hospital stay (inpatient length of stay)	£26,576	£24,227	£2,349
7	Unit cost: Hospital stay (inpatient length of stay)	£26,576	£24,227	£2,349
8	Tx disc beyond 52w: Dupilumab + Background Therapy	£26,588	£24,498	£2,090
9	Whittaker 2022 IRR, 1 severe exacerbation history: severe exacerbation	£26,423	£24,525	£1,898
10	FEV change, Fenwick, To Sev, Mod ex	£26,568	£24,709	£1,859

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; ICER = incremental cost-effectiveness ratio; IRR = incidence rate ratio; QALY = quality-adjusted life year

Scenario analysis

Table 62. Corresponding to Table 80 in the CS. Scenario analysis results – PAS price

Parameter	Scenario	Incr. QALYs	Incr. costs	ICER*	Rationale
Base case	**N/A**	[redacted]	[redacted]	25,515	**N/A**
		[redacted]	[redacted]	23,518	
Discount, cost	3%	[redacted]	[redacted]	25,975	Alternative input to the NICE reference case.
		[redacted]	[redacted]	24,292	
	5%	[redacted]	[redacted]	24,257	
		[redacted]	[redacted]	22,480	
Discount, health	3%	[redacted]	[redacted]	24,574	
		[redacted]	[redacted]	22,857	
	5%	[redacted]	[redacted]	28,438	
		[redacted]	[redacted]	26,467	
Time horizon	5 years	[redacted]	[redacted]	59,894	
		[redacted]	[redacted]	54,948	
	10 years	[redacted]	[redacted]	33,910	
		[redacted]	[redacted]	31,296	
	20 years	[redacted]	[redacted]	25,853	
		[redacted]	[redacted]	24,274	
Annual discontinuation rate beyond 52 weeks	22.4%	[redacted]	[redacted]	£22,832	This percentage is derived from the average discontinuation rate of biologic therapy from UK Severe Asthma Registry identified by Mansur et al. 2022.(32)
		[redacted]	[redacted]	£20,889	
	25.84%	[redacted]	[redacted]	£21,873	This scenario represents the views of clinical experts gathered through a structured expert elicitation.
		[redacted]	[redacted]	£19,885	
FEV_1 treatment effect duration	Dupilumab + background therapy - 1 years; background therapy - 0 year	[redacted]	[redacted]	£27,704	This scenario represents the views of clinical experts gathered through a structured expert elicitation.
		[redacted]	[redacted]	£25,391	
Baseline exacerbation rate	Background therapy - RWE; Dupilumab + background therapy - RR vs background therapy alone	[redacted]	[redacted]	£25,769	To reflect real-world exacerbation rates from Type 2 uncontrolled COPD patients in the UK.
		[redacted]	[redacted]	£23,731	
	Background therapy – Pooled BOREAS and NOTUS (taken during	[redacted]	[redacted]	£28,738	Exploratory scenario utilising in-trial exacerbation rates.

Parameter	Scenario	Incr. QALYs	Incr. costs	ICER*	Rationale
	the trial); Dupilumab + background therapy - RR vs background therapy alone	[redacted]	[redacted]	£27,836	
Markov transition probabilities (transitions related to exacerbation)	Background therapy - Pooled BOREAS and NOTUS; Dupilumab + background therapy - RR vs background therapy alone With pooled ITT baseline exacerbation taken during the trial	[redacted]	[redacted]	£46,244	Exploratory scenario using trial data. This scenario is considered extreme because studies have shown that cumulative prior exacerbations can predict future exacerbations.
		[redacted]	[redacted]	£46,895	
Utilities	Mean adjusted CFB (LS-Regression-CW-NOTUS) for COPD as well as exacerbation disutilities	[redacted]	[redacted]	£26,100	Utility values based on trial data from NOTUS EQ-5D-5L, using the UK crosswalk tariff (Hernandez 2020), taken from Week 24 and 52 only.
		[redacted]	[redacted]	£24,040	
	Spencer et al. 2005 & Sadatsafavi et al. 2019 with exacerbation disutilities from Rutten Van Molken et al. 2009	[redacted]	[redacted]	£26,784	Alternative source from published literature.
		[redacted]	[redacted]	£24,391	
	Rutten Van Molken et al. 2006 with exacerbation disutilities from Rutten Van Molken et al. 2009	[redacted]	[redacted]	£25,294	The utility value is derived from published literature and aligns with the utility source from NICE NG115 COPD economic model report.
		[redacted]	[redacted]	£23,393	
	Borg et al. 2004 with exacerbation disutilities from Rutten Van Molken et al. 2009	[redacted]	[redacted]	£24,642	Alternative source from published literature.
		[redacted]	[redacted]	£22,426	
Excess mortality due to GOLD severity	Shavelle et al. 2009	[redacted]	[redacted]	£25,683	Shavelle et al. 2009 was used as an alternative mortality source from published literature, with mortality stratified based on non-exacerbation-related mortality as per Trigueros et al.
		[redacted]	[redacted]	£23,589	
	Leivseth et al. 2013	[redacted]	[redacted]	£25,810	An alternative mortality source from a Norwegian RWE study involving 1,540 patients, which was utilised in the NICE
		[redacted]	[redacted]	£23,467	

Parameter	Scenario	Incr. QALYs	Incr. costs	ICER*	Rationale
					NG145 guideline model report.
Excess mortality due to exacerbation	Whittaker et al. 2022	[redacted]	[redacted]	£36,449	An alternative source that provides mortality rates for both moderate and severe exacerbations.
		[redacted]	[redacted]	£33,331	
FEV_1 treatment effect beyond the trial	Unadjusted FEV_1 trajectory according to Fenwick	[redacted]	[redacted]	£26,970	To reflect the transitions from the original Fenwick equation without modifications, representing the accelerated FEV_1 decline in patients with Type 2 inflammation.
		[redacted]	[redacted]	£24,481	
Societal impact	Include societal perspective comprising loss of productivity and early retirement for patients only	[redacted]	[redacted]	£25,635	To reflect the potential impact on wider society
		[redacted]	[redacted]	£24,345	

*The deterministic ICER is first followed by the probabilistic ICER in each category. CFB = change from baseline; COPD = chronic obstructive pulmonary disease; CW = crosswalk; EQ-5D-5L = EuroQoL 5-Dimensions 5-Level; FEV_1 = forced expiratory volume in 1 second; ICER = incremental cost-effectiveness ratio; ITT = intent-to-treat; LS = least squares; N/A= not applicable; NICE = National Institute for Health and Care Excellence; PAS = patient access scheme; RR = risk ratio; RWE = real world evidence; UK = United Kingdom

Subgroup analysis

Table 63. Corresponding to Table 84 in the CS. Incremental cost-effectiveness results for the subgroup with FeNO ≥20 ppb

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Probabilistic analysis							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,931
Background Therapy	[redacted]	[redacted]	[redacted]				
Deterministic analysis							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,913
Background Therapy	[redacted]	[redacted]	[redacted]				

FeNO = fractional exhaled nitric oxide; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Figure 17. Corresponding to Figure 36 in the CS. Scatter plot for incremental cost-effectiveness for the subgroup with FeNO ≥20 ppb (1,000 iterations)


[redacted]

FeNO = fractional exhaled nitric oxide; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 18. Corresponding to Figure 37 in the CS. Cost-effectiveness acceptability curve for the subgroup with FeNO ≥20 ppb (1,000 iterations)

Table 64. Corresponding to Table 85 in the CS. Incremental cost-effectiveness results for the subgroup with EOS ≥500 cells/µL

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Probabilistic Analysis							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,483
Background Therapy	[redacted]	[redacted]	[redacted]				
Deterministic analysis							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,473
Background Therapy	[redacted]	[redacted]	[redacted]				

EOS = eosinophils; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Figure 19. Corresponding to Figure 38 in the CS. Scatter plot for incremental cost-effectiveness for the subgroup with EOS ≥500 cells/µL (1,000 iterations)

EOS = eosinophils; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 20. Corresponding to Figure 39 in the CS. Cost-effectiveness acceptability curve for the subgroup with EOS ≥500 cells/µL (1,000 iterations)

Appendix 3. Adverse Events

Table 65. Number (%) of participants with treatment emergent severe AEs and Treatment emergent serious AEs by Primary SOC, HLGT, HLT and PT

PRIMARY SYSTEM ORGAN CLASS	Placebo	Dupilumab
HLGT: High Level Group Term	(N=934)	(N=938)
HLT: High Level Term		
Preferred Term n(%)		
Treatment emergent serious AEs		

PRIMARY SYSTEM ORGAN CLASS	Placebo	Dupilumab
Any Class	[redacted]	[redacted]
INFECTIONS AND INFESTATIONS	[redacted]	[redacted]
HLGT: Bacterial infectious disorders	[redacted]	[redacted]
HLT: Bacterial infections NEC	[redacted]	[redacted]
Bacterial colitis	[redacted]	[redacted]
Lower respiratory tract infection bacterial	[redacted]	[redacted]
Pneumonia bacterial	[redacted]	[redacted]
Respiratory tract infection bacterial	[redacted]	[redacted]
HLT: Klebsiella infections	[redacted]	[redacted]
Pneumonia klebsiella	[redacted]	[redacted]
HLT: Pseudomonal infections	[redacted]	[redacted]
Pneumonia pseudomonal	[redacted]	[redacted]
HLT: Streptococcal infections	[redacted]	[redacted]
Pneumonia pneumococcal	[redacted]	[redacted]
HLGT: Fungal infectious disorders	[redacted]	[redacted]
HLT: Tinea infections	[redacted]	[redacted]
Tinea pedis	[redacted]	[redacted]
HLGT: Infections - pathogen unspecified	[redacted]	[redacted]
HLT: Abdominal and gastrointestinal infections	[redacted]	[redacted]
Diverticulitis	[redacted]	[redacted]
Gastrointestinal infection	[redacted]	[redacted]
HLT: Bone and joint infections	[redacted]	[redacted]
Bursitis infective	[redacted]	[redacted]
HLT: Eye and eyelid infections	[redacted]	[redacted]
Conjunctivitis	[redacted]	[redacted]
HLT: Hepatobiliary and spleen infections	[redacted]	[redacted]
Cholecystitis infective	[redacted]	[redacted]
HLT: Lower respiratory tract and lung infections	[redacted]	[redacted]
Infective exacerbation of chronic obstructive airways disease	[redacted]	[redacted]
Lower respiratory tract infection	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
HLT: Male reproductive tract infections	[redacted]	[redacted]
Orchitis	[redacted]	[redacted]
HLT: Sepsis, bacteraemia, viraemia and fungaemia NEC	[redacted]	[redacted]
Septic shock	[redacted]	[redacted]
HLT: Upper respiratory tract infections	[redacted]	[redacted]
Epiglottitis	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
HLT: Urinary tract infections	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
HLGT: Viral infectious disorders	[redacted]	[redacted]
HLT: Coronavirus infections	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]

PRIMARY SYSTEM ORGAN CLASS	Placebo	Dupilumab
Suspected COVID-19	[redacted]	[redacted]
HLT: Herpes viral infections	[redacted]	[redacted]
Ophthalmic herpes zoster	[redacted]	[redacted]
HLT: Influenza viral infections	[redacted]	[redacted]
Influenza	[redacted]	[redacted]
HLT: Viral infections NEC	[redacted]	[redacted]
Viral upper respiratory tract infection	[redacted]	[redacted]
	[redacted]	[redacted]
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	[redacted]	[redacted]
HLGT: Breast neoplasms malignant and unspecified (incl nipple)	[redacted]	[redacted]
HLT: Breast and nipple neoplasms malignant	[redacted]	[redacted]
Invasive ductal breast carcinoma	[redacted]	[redacted]
HLGT: Gastrointestinal neoplasms malignant and unspecified	[redacted]	[redacted]
HLT: Colorectal neoplasms malignant	[redacted]	[redacted]
Adenocarcinoma of colon	[redacted]	[redacted]
Rectal cancer	[redacted]	[redacted]
HLT: Pancreatic neoplasms malignant (excl islet cell and carcinoid)	[redacted]	[redacted]
Ductal adenocarcinoma of pancreas	[redacted]	[redacted]
Pancreatic carcinoma metastatic	[redacted]	[redacted]
HLGT: Nervous system neoplasms malignant and unspecified NEC	[redacted]	[redacted]
HLT: Glial tumours malignant	[redacted]	[redacted]
Glioblastoma	[redacted]	[redacted]
HLGT: Renal and urinary tract neoplasms malignant and unspecified	[redacted]	[redacted]
HLT: Urinary tract neoplasms unspecified malignancy NEC	[redacted]	[redacted]
Bladder neoplasm	[redacted]	[redacted]
HLGT: Respiratory and mediastinal neoplasms malignant and unspecified	[redacted]	[redacted]
HLT: Non-small cell neoplasms malignant of the respiratory tract cell type specified	[redacted]	[redacted]
Lung adenocarcinoma	[redacted]	[redacted]
Squamous cell carcinoma of lung	[redacted]	[redacted]
HLT: Respiratory tract and pleural neoplasms malignancy unspecified NEC	[redacted]	[redacted]
Lung neoplasm	[redacted]	[redacted]
HLT: Respiratory tract and pleural neoplasms malignant cell type unspecified NEC	[redacted]	[redacted]
Lung neoplasm malignant	[redacted]	[redacted]
	[redacted]	[redacted]
BLOOD AND LYMPHATIC SYSTEM DISORDERS	[redacted]	[redacted]
HLGT: Anaemias nonhaemolytic and marrow depression	[redacted]	[redacted]
HLT: Anaemia deficiencies	[redacted]	[redacted]
Iron deficiency anaemia	[redacted]	[redacted]
HLT: Anaemias NEC	[redacted]	[redacted]
Blood loss anaemia	[redacted]	[redacted]
HLGT: Haemolyses and related conditions	[redacted]	[redacted]
HLT: Anaemias haemolytic immune	[redacted]	[redacted]
Autoimmune haemolytic anaemia	[redacted]	[redacted]

PRIMARY SYSTEM ORGAN CLASS	Placebo	Dupilumab
HLGT: Red blood cell disorders	[redacted]	[redacted]
HLT: Polycythaemia (excl rubra vera)	[redacted]	[redacted]
Polycythaemia	[redacted]	[redacted]
HLGT: White blood cell disorders	[redacted]	[redacted]
HLT: Eosinophilic disorders	[redacted]	[redacted]
Eosinophilia	[redacted]	[redacted]
	[redacted]	[redacted]
IMMUNE SYSTEM DISORDERS	[redacted]	[redacted]
HLGT: Allergic conditions	[redacted]	[redacted]
HLT: Allergic conditions NEC	[redacted]	[redacted]
Hypersensitivity	[redacted]	[redacted]
HLT: Anaphylactic and anaphylactoid responses	[redacted]	[redacted]
Anaphylactic reaction	[redacted]	[redacted]
	[redacted]	[redacted]
ENDOCRINE DISORDERS	[redacted]	[redacted]
HLGT: Hypothalamus and pituitary gland disorders	[redacted]	[redacted]
HLT: Posterior pituitary disorders	[redacted]	[redacted]
Inappropriate antidiuretic hormone secretion	[redacted]	[redacted]
	[redacted]	[redacted]
METABOLISM AND NUTRITION DISORDERS	[redacted]	[redacted]
HLGT: Electrolyte and fluid balance conditions	[redacted]	[redacted]
HLT: Potassium imbalance	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
HLT: Sodium imbalance	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]
HLGT: Glucose metabolism disorders (incl diabetes mellitus)	[redacted]	[redacted]
HLT: Diabetes mellitus (incl subtypes)	[redacted]	[redacted]
Diabetes mellitus	[redacted]	[redacted]
Diabetes mellitus inadequate control	[redacted]	[redacted]
Type 2 diabetes mellitus	[redacted]	[redacted]
	[redacted]	[redacted]
PSYCHIATRIC DISORDERS	[redacted]	[redacted]
HLGT: Schizophrenia and other psychotic disorders	[redacted]	[redacted]
HLT: Psychotic disorder NEC	[redacted]	[redacted]
Psychotic disorder	[redacted]	[redacted]
	[redacted]	[redacted]
NERVOUS SYSTEM DISORDERS	[redacted]	[redacted]
HLGT: Central nervous system vascular disorders	[redacted]	[redacted]
HLT: Central nervous system haemorrhages and cerebrovascular accidents	[redacted]	[redacted]
Basal ganglia haemorrhage	[redacted]	[redacted]
Cerebral haemorrhage	[redacted]	[redacted]
Cerebral infarction	[redacted]	[redacted]
Cerebrovascular accident	[redacted]	[redacted]
Ischaemic stroke	[redacted]	[redacted]

PRIMARY SYSTEM ORGAN CLASS	Placebo	Dupilumab
HLGT: Cranial nerve disorders (excl neoplasms)	[redacted]	[redacted]
HLT: Vagus nerve disorders	[redacted]	[redacted]
Vocal cord paralysis	[redacted]	[redacted]
HLGT: Headaches	[redacted]	[redacted]
HLT: Headaches NEC	[redacted]	[redacted]
Headache	[redacted]	[redacted]
HLGT: Neurological disorders NEC	[redacted]	[redacted]
HLT: Disturbances in consciousness NEC	[redacted]	[redacted]
Syncope	[redacted]	[redacted]
	[redacted]	[redacted]
EYE DISORDERS	[redacted]	[redacted]
HLGT: Ocular infections, irritations and inflammations	[redacted]	[redacted]
HLT: Corneal infections, oedemas and inflammations	[redacted]	[redacted]
Keratitis	[redacted]	[redacted]
	[redacted]	[redacted]
CARDIAC DISORDERS	[redacted]	[redacted]
HLGT: Cardiac arrhythmias	[redacted]	[redacted]
HLT: Cardiac conduction disorders	[redacted]	[redacted]
Atrioventricular block complete	[redacted]	[redacted]
HLT: Rate and rhythm disorders NEC	[redacted]	[redacted]
Arrhythmia	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]
Tachycardia	[redacted]	[redacted]
HLT: Supraventricular arrhythmias	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]
Sinus node dysfunction	[redacted]	[redacted]
Supraventricular tachycardia	[redacted]	[redacted]
HLT: Ventricular arrhythmias and cardiac arrest	[redacted]	[redacted]
Cardiac arrest	[redacted]	[redacted]
Ventricular arrhythmia	[redacted]	[redacted]
HLGT: Cardiac disorders, signs and symptoms NEC	[redacted]	[redacted]
HLT: Cardiac disorders NEC	[redacted]	[redacted]
Cardiovascular disorder	[redacted]	[redacted]
HLGT: Cardiac valve disorders	[redacted]	[redacted]
HLT: Mitral valvular disorders	[redacted]	[redacted]
Mitral valve incompetence	[redacted]	[redacted]
HLGT: Coronary artery disorders	[redacted]	[redacted]
HLT: Coronary artery disorders NEC	[redacted]	[redacted]
Coronary artery disease	[redacted]	[redacted]
HLT: Ischaemic coronary artery disorders	[redacted]	[redacted]
Acute coronary syndrome	[redacted]	[redacted]
Acute myocardial infarction	[redacted]	[redacted]
Angina pectoris	[redacted]	[redacted]
Angina unstable	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]

PRIMARY SYSTEM ORGAN CLASS	Placebo	Dupilumab
Myocardial ischaemia	[redacted]	[redacted]
HLGT: Heart failures	[redacted]	[redacted]
HLT: Heart failures NEC	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]
Cardiac failure congestive	[redacted]	[redacted]
Cardiogenic shock	[redacted]	[redacted]
HLT: Right ventricular failures	[redacted]	[redacted]
Cor pulmonale	[redacted]	[redacted]
Cor pulmonale acute	[redacted]	[redacted]
	[redacted]	[redacted]
VASCULAR DISORDERS	[redacted]	[redacted]
HLGT: Arteriosclerosis, stenosis, vascular insufficiency and necrosis	[redacted]	[redacted]
HLT: Peripheral vasoconstriction, necrosis and vascular insufficiency	[redacted]	[redacted]
Extremity necrosis	[redacted]	[redacted]
Peripheral arterial occlusive disease	[redacted]	[redacted]
Peripheral artery occlusion	[redacted]	[redacted]
HLGT: Decreased and nonspecific blood pressure disorders and shock	[redacted]	[redacted]
HLT: Vascular hypotensive disorders	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]
HLGT: Embolism and thrombosis	[redacted]	[redacted]
HLT: Peripheral embolism and thrombosis	[redacted]	[redacted]
Deep vein thrombosis	[redacted]	[redacted]
HLGT: Vascular disorders NEC	[redacted]	[redacted]
HLT: Peripheral vascular disorders NEC	[redacted]	[redacted]
Peripheral vascular disorder	[redacted]	[redacted]
HLGT: Vascular hypertensive disorders	[redacted]	[redacted]
HLT: Accelerated and malignant hypertension	[redacted]	[redacted]
Hypertensive emergency	[redacted]	[redacted]
	[redacted]	[redacted]
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	[redacted]	[redacted]
HLGT: Bronchial disorders (excl neoplasms)	[redacted]	[redacted]
HLT: Bronchospasm and obstruction	[redacted]	[redacted]
Bronchospasm	[redacted]	[redacted]
Chronic obstructive pulmonary disease	[redacted]	[redacted]
HLGT: Lower respiratory tract disorders (excl obstruction and infection)	[redacted]	[redacted]
HLT: Parenchymal lung disorders NEC	[redacted]	[redacted]
Atelectasis	[redacted]	[redacted]
HLT: Pulmonary oedemas	[redacted]	[redacted]
Pulmonary oedema	[redacted]	[redacted]
HLGT: Pleural disorders	[redacted]	[redacted]
HLT: Pleural infections and inflammations	[redacted]	[redacted]
Pleurisy	[redacted]	[redacted]
HLT: Pneumothorax and pleural effusions NEC	[redacted]	[redacted]
Hydrothorax	[redacted]	[redacted]
Pneumothorax	[redacted]	[redacted]

PRIMARY SYSTEM ORGAN CLASS	Placebo	Dupilumab
HLGT: Pulmonary vascular disorders	[redacted]	[redacted]
HLT: Pulmonary hypertensions	[redacted]	[redacted]
Pulmonary hypertension	[redacted]	[redacted]
HLGT: Respiratory disorders NEC	[redacted]	[redacted]
HLT: Respiratory failures (excl neonatal)	[redacted]	[redacted]
Acute respiratory failure	[redacted]	[redacted]
Chronic respiratory failure	[redacted]	[redacted]
Respiratory failure	[redacted]	[redacted]
	[redacted]	[redacted]
GASTROINTESTINAL DISORDERS	[redacted]	[redacted]
HLGT: Abdominal hernias and other abdominal wall conditions	[redacted]	[redacted]
HLT: Abdominal hernias NEC	[redacted]	[redacted]
Abdominal hernia	[redacted]	[redacted]
HLGT: Benign neoplasms gastrointestinal	[redacted]	[redacted]
HLT: Benign neoplasms gastrointestinal (excl oral cavity)	[redacted]	[redacted]
Intestinal polyp	[redacted]	[redacted]
HLGT: Exocrine pancreas conditions	[redacted]	[redacted]
HLT: Acute and chronic pancreatitis	[redacted]	[redacted]
Pancreatitis	[redacted]	[redacted]
Pancreatitis acute	[redacted]	[redacted]
HLGT: Gastrointestinal signs and symptoms	[redacted]	[redacted]
HLT: Gastrointestinal and abdominal pains (excl oral and throat)	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]
HLGT: Gastrointestinal stenosis and obstruction	[redacted]	[redacted]
HLT: Gastrointestinal stenosis and obstruction NEC	[redacted]	[redacted]
Subileus	[redacted]	[redacted]
HLT: Large intestinal stenosis and obstruction	[redacted]	[redacted]
Large intestinal stenosis	[redacted]	[redacted]
HLGT: Gastrointestinal vascular conditions	[redacted]	[redacted]
HLT: Gastrointestinal vascular occlusion and infarction	[redacted]	[redacted]
Intestinal ischaemia	[redacted]	[redacted]
	[redacted]	[redacted]
HEPATOBILIARY DISORDERS	[redacted]	[redacted]
HLGT: Bile duct disorders	[redacted]	[redacted]
HLT: Obstructive bile duct disorders (excl neoplasms)	[redacted]	[redacted]
Bile duct stone	[redacted]	[redacted]
HLGT: Gallbladder disorders	[redacted]	[redacted]
HLT: Cholecystitis and cholelithiasis	[redacted]	[redacted]
Cholecystitis	[redacted]	[redacted]
Cholecystitis acute	[redacted]	[redacted]
HLGT: Hepatic and hepatobiliary disorders	[redacted]	[redacted]
HLT: Hepatic failure and associated disorders	[redacted]	[redacted]
Hepatic failure	[redacted]	[redacted]
Hepatorenal syndrome	[redacted]	[redacted]
	[redacted]	[redacted]

PRIMARY SYSTEM ORGAN CLASS	Placebo	Dupilumab
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	[redacted]	[redacted]
HLGT: Skin and subcutaneous tissue disorders NEC	[redacted]	[redacted]
HLT: Skin and subcutaneous tissue ulcerations	[redacted]	[redacted]
Diabetic wound	[redacted]	[redacted]
	[redacted]	[redacted]
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	[redacted]	[redacted]
HLGT: Muscle disorders	[redacted]	[redacted]
HLT: Myopathies	[redacted]	[redacted]
Rhabdomyolysis	[redacted]	[redacted]
HLGT: Musculoskeletal and connective tissue disorders NEC	[redacted]	[redacted]
HLT: Musculoskeletal and connective tissue conditions NEC	[redacted]	[redacted]
Dupuytren's contracture	[redacted]	[redacted]
	[redacted]	[redacted]
RENAL AND URINARY DISORDERS	[redacted]	[redacted]
HLGT: Nephropathies	[redacted]	[redacted]
HLT: Nephritis NEC	[redacted]	[redacted]
Nephritis	[redacted]	[redacted]
HLGT: Renal disorders (excl nephropathies)	[redacted]	[redacted]
HLT: Renal failure and impairment	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]
Renal failure	[redacted]	[redacted]
	[redacted]	[redacted]
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	[redacted]	[redacted]
HLGT: Administration site reactions	[redacted]	[redacted]
HLT: Injection site reactions	[redacted]	[redacted]
Injection site rash	[redacted]	[redacted]
HLGT: Fatal outcomes	[redacted]	[redacted]
HLT: Death and sudden death	[redacted]	[redacted]
Death	[redacted]	[redacted]
Sudden cardiac death	[redacted]	[redacted]
Sudden death	[redacted]	[redacted]
HLGT: General system disorders NEC	[redacted]	[redacted]
HLT: Pain and discomfort NEC	[redacted]	[redacted]
Chest pain	[redacted]	[redacted]
Non-cardiac chest pain	[redacted]	[redacted]
	[redacted]	[redacted]
INVESTIGATIONS	[redacted]	[redacted]
HLGT: Enzyme investigations NEC	[redacted]	[redacted]
HLT: Skeletal and cardiac muscle analyses	[redacted]	[redacted]
Troponin increased	[redacted]	[redacted]
	[redacted]	[redacted]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	[redacted]	[redacted]
HLGT: Bone and joint injuries	[redacted]	[redacted]
HLT: Limb fractures and dislocations	[redacted]	[redacted]
Ankle fracture	[redacted]	[redacted]

PRIMARY SYSTEM ORGAN CLASS	Placebo	Dupilumab
Femoral neck fracture	[redacted]	[redacted]
Femur fracture	[redacted]	[redacted]
Fibula fracture	[redacted]	[redacted]
Tibia fracture	[redacted]	[redacted]
Wrist fracture	[redacted]	[redacted]
HLT: Thoracic cage fractures and dislocations	[redacted]	[redacted]
Rib fracture	[redacted]	[redacted]
HLGT: Injuries NEC	[redacted]	[redacted]
HLT: Cerebral injuries NEC	[redacted]	[redacted]
Brain contusion	[redacted]	[redacted]
HLT: Chest and respiratory tract injuries NEC	[redacted]	[redacted]
Pneumothorax traumatic	[redacted]	[redacted]
HLT: Eye injuries NEC	[redacted]	[redacted]
Periorbital haematoma	[redacted]	[redacted]
HLT: Muscle, tendon and ligament injuries	[redacted]	[redacted]
Ligament sprain	[redacted]	[redacted]
HLT: Non-site specific injuries NEC	[redacted]	[redacted]
Fall	[redacted]	[redacted]
Road traffic accident	[redacted]	[redacted]
HLT: Skin injuries NEC	[redacted]	[redacted]
Contusion	[redacted]	[redacted]
HLGT: Injuries by physical agents	[redacted]	[redacted]
HLT: Thermal burns	[redacted]	[redacted]
Thermal burn	[redacted]	[redacted]
Treatment emergent serious AEs		
Any Class	[redacted]	[redacted]
INFECTIONS AND INFESTATIONS	[redacted]	[redacted]
HLGT: Bacterial infectious disorders	[redacted]	[redacted]
HLT: Bacterial infections NEC	[redacted]	[redacted]
Bacterial colitis	[redacted]	[redacted]
Bronchitis bacterial	[redacted]	[redacted]
Lower respiratory tract infection bacterial	[redacted]	[redacted]
Pneumonia bacterial	[redacted]	[redacted]
HLT: Clostridia infections	[redacted]	[redacted]
Clostridium difficile colitis	[redacted]	[redacted]
HLT: Klebsiella infections	[redacted]	[redacted]
Pneumonia klebsiella	[redacted]	[redacted]
HLT: Pseudomonal infections	[redacted]	[redacted]
Pneumonia pseudomonal	[redacted]	[redacted]
HLT: Streptococcal infections	[redacted]	[redacted]
Pneumonia pneumococcal	[redacted]	[redacted]
Pneumonia streptococcal	[redacted]	[redacted]
HLGT: Fungal infectious disorders	[redacted]	[redacted]
HLT: Aspergillus infections	[redacted]	[redacted]
Bronchopulmonary aspergillosis	[redacted]	[redacted]

PRIMARY SYSTEM ORGAN CLASS	Placebo	Dupilumab
HLT: Candida infections	[redacted]	[redacted]
Nasal candidiasis	[redacted]	[redacted]
Oropharyngeal candidiasis	[redacted]	[redacted]
HLGT: Infections - pathogen unspecified	[redacted]	[redacted]
HLT: Abdominal and gastrointestinal infections	[redacted]	[redacted]
Abdominal wall abscess	[redacted]	[redacted]
Anal abscess	[redacted]	[redacted]
Appendicitis	[redacted]	[redacted]
Diverticulitis	[redacted]	[redacted]
Gastrointestinal infection	[redacted]	[redacted]
HLT: Hepatobiliary and spleen infections	[redacted]	[redacted]
Cholecystitis infective	[redacted]	[redacted]
HLT: Infections NEC	[redacted]	[redacted]
Respiratory tract infection	[redacted]	[redacted]
HLT: Lower respiratory tract and lung infections	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]
Infective exacerbation of chronic obstructive airways disease	[redacted]	[redacted]
Lower respiratory tract infection	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
HLT: Male reproductive tract infections	[redacted]	[redacted]
Orchitis	[redacted]	[redacted]
HLT: Sepsis, bacteraemia, viraemia and fungaemia NEC	[redacted]	[redacted]
Septic shock	[redacted]	[redacted]
HLT: Skin structures and soft tissue infections	[redacted]	[redacted]
Subcutaneous abscess	[redacted]	[redacted]
HLT: Upper respiratory tract infections	[redacted]	[redacted]
Epiglottitis	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
HLT: Urinary tract infections	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
HLGT: Mycobacterial infectious disorders	[redacted]	[redacted]
HLT: Tuberculous infections	[redacted]	[redacted]
Pulmonary tuberculosis	[redacted]	[redacted]
HLGT: Viral infectious disorders	[redacted]	[redacted]
HLT: Coronavirus infections	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]
Suspected COVID-19	[redacted]	[redacted]
HLT: Herpes viral infections	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]
HLT: Influenza viral infections	[redacted]	[redacted]
Influenza	[redacted]	[redacted]
HLT: Viral infections NEC	[redacted]	[redacted]
Viral upper respiratory tract infection	[redacted]	[redacted]
	[redacted]	[redacted]

PRIMARY SYSTEM ORGAN CLASS	Placebo	Dupilumab
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	[redacted]	[redacted]
HLGT: Breast neoplasms malignant and unspecified (incl nipple)	[redacted]	[redacted]
HLT: Breast and nipple neoplasms malignant	[redacted]	[redacted]
Invasive ductal breast carcinoma	[redacted]	[redacted]
HLGT: Endocrine neoplasms malignant and unspecified	[redacted]	[redacted]
HLT: Thyroid neoplasms malignant	[redacted]	[redacted]
Papillary thyroid cancer	[redacted]	[redacted]
HLGT: Gastrointestinal neoplasms malignant and unspecified	[redacted]	[redacted]
HLT: Colorectal neoplasms malignant	[redacted]	[redacted]
Adenocarcinoma of colon	[redacted]	[redacted]
Rectal cancer	[redacted]	[redacted]
HLT: Pancreatic neoplasms malignant (excl islet cell and carcinoid)	[redacted]	[redacted]
Ductal adenocarcinoma of pancreas	[redacted]	[redacted]
Pancreatic carcinoma metastatic	[redacted]	[redacted]
HLGT: Leukaemias	[redacted]	[redacted]
HLT: Myelodysplastic syndromes	[redacted]	[redacted]
Chronic myelomonocytic leukaemia	[redacted]	[redacted]
HLGT: Nervous system neoplasms malignant and unspecified NEC	[redacted]	[redacted]
HLT: Glial tumours malignant	[redacted]	[redacted]
Glioblastoma	[redacted]	[redacted]
HLGT: Renal and urinary tract neoplasms malignant and unspecified	[redacted]	[redacted]
HLT: Bladder neoplasms malignant	[redacted]	[redacted]
Bladder transitional cell carcinoma	[redacted]	[redacted]
HLGT: Reproductive neoplasms male malignant and unspecified	[redacted]	[redacted]
HLT: Prostatic neoplasms malignant	[redacted]	[redacted]
Prostate cancer	[redacted]	[redacted]
HLGT: Respiratory and mediastinal neoplasms malignant and unspecified	[redacted]	[redacted]
HLT: Non-small cell neoplasms malignant of the respiratory tract cell type specified	[redacted]	[redacted]
Lung adenocarcinoma	[redacted]	[redacted]
Squamous cell carcinoma of lung	[redacted]	[redacted]
HLT: Respiratory tract and pleural neoplasms malignancy unspecified NEC	[redacted]	[redacted]
Lung neoplasm	[redacted]	[redacted]
HLT: Respiratory tract and pleural neoplasms malignant cell type unspecified NEC	[redacted]	[redacted]
Lung carcinoma cell type unspecified stage IV	[redacted]	[redacted]
Lung neoplasm malignant	[redacted]	[redacted]
HLGT: Skin neoplasms malignant and unspecified	[redacted]	[redacted]
HLT: Skin neoplasms malignant and unspecified (excl melanoma)	[redacted]	[redacted]
Squamous cell carcinoma of skin	[redacted]	[redacted]
	[redacted]	[redacted]
BLOOD AND LYMPHATIC SYSTEM DISORDERS	[redacted]	[redacted]
HLGT: Anaemias nonhaemolytic and marrow depression	[redacted]	[redacted]
HLT: Anaemia deficiencies	[redacted]	[redacted]
Iron deficiency anaemia	[redacted]	[redacted]

PRIMARY SYSTEM ORGAN CLASS	Placebo	Dupilumab
HLT: Anaemias NEC	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Blood loss anaemia	[redacted]	[redacted]
HLGT: Haemolyses and related conditions	[redacted]	[redacted]
HLT: Anaemias haemolytic immune	[redacted]	[redacted]
Autoimmune haemolytic anaemia	[redacted]	[redacted]
HLGT: Red blood cell disorders	[redacted]	[redacted]
HLT: Polycythaemia (excl rubra vera)	[redacted]	[redacted]
Polycythaemia	[redacted]	[redacted]
	[redacted]	[redacted]
IMMUNE SYSTEM DISORDERS	[redacted]	[redacted]
HLGT: Allergic conditions	[redacted]	[redacted]
HLT: Allergic conditions NEC	[redacted]	[redacted]
Hypersensitivity	[redacted]	[redacted]
HLT: Anaphylactic and anaphylactoid responses	[redacted]	[redacted]
Anaphylactic reaction	[redacted]	[redacted]
	[redacted]	[redacted]
ENDOCRINE DISORDERS	[redacted]	[redacted]
HLGT: Hypothalamus and pituitary gland disorders	[redacted]	[redacted]
HLT: Posterior pituitary disorders	[redacted]	[redacted]
Inappropriate antidiuretic hormone secretion	[redacted]	[redacted]
HLGT: Parathyroid gland disorders	[redacted]	[redacted]
HLT: Hyperparathyroid disorders	[redacted]	[redacted]
Hyperparathyroidism	[redacted]	[redacted]
	[redacted]	[redacted]
METABOLISM AND NUTRITION DISORDERS	[redacted]	[redacted]
HLGT: Appetite and general nutritional disorders	[redacted]	[redacted]
HLT: Appetite disorders	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
HLGT: Electrolyte and fluid balance conditions	[redacted]	[redacted]
HLT: Potassium imbalance	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
HLT: Sodium imbalance	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]
HLGT: Glucose metabolism disorders (incl diabetes mellitus)	[redacted]	[redacted]
HLT: Diabetes mellitus (incl subtypes)	[redacted]	[redacted]
Diabetes mellitus inadequate control	[redacted]	[redacted]
Type 2 diabetes mellitus	[redacted]	[redacted]
	[redacted]	[redacted]
PSYCHIATRIC DISORDERS	[redacted]	[redacted]
HLGT: Schizophrenia and other psychotic disorders	[redacted]	[redacted]
HLT: Psychotic disorder NEC	[redacted]	[redacted]
Psychotic disorder	[redacted]	[redacted]
	[redacted]	[redacted]

PRIMARY SYSTEM ORGAN CLASS	Placebo	Dupilumab
NERVOUS SYSTEM DISORDERS	[redacted]	[redacted]
HLGT: Central nervous system vascular disorders	[redacted]	[redacted]
HLT: Central nervous system haemorrhages and cerebrovascular accidents	[redacted]	[redacted]
Basal ganglia haemorrhage	[redacted]	[redacted]
Cerebral haemorrhage	[redacted]	[redacted]
Cerebral infarction	[redacted]	[redacted]
Cerebrovascular accident	[redacted]	[redacted]
Ischaemic stroke	[redacted]	[redacted]
Lacunar stroke	[redacted]	[redacted]
HLT: Transient cerebrovascular events	[redacted]	[redacted]
Transient ischaemic attack	[redacted]	[redacted]
HLGT: Cranial nerve disorders (excl neoplasms)	[redacted]	[redacted]
HLT: Vagus nerve disorders	[redacted]	[redacted]
Vocal cord paralysis	[redacted]	[redacted]
HLGT: Headaches	[redacted]	[redacted]
HLT: Headaches NEC	[redacted]	[redacted]
Headache	[redacted]	[redacted]
HLGT: Neurological disorders NEC	[redacted]	[redacted]
HLT: Disturbances in consciousness NEC	[redacted]	[redacted]
Syncope	[redacted]	[redacted]
HLT: Neurological signs and symptoms NEC	[redacted]	[redacted]
Presyncope	[redacted]	[redacted]
HLGT: Seizures (incl subtypes)	[redacted]	[redacted]
HLT: Generalised tonic-clonic seizures	[redacted]	[redacted]
Generalised tonic-clonic seizure	[redacted]	[redacted]
	[redacted]	[redacted]
EYE DISORDERS	[redacted]	[redacted]
HLGT: Anterior eye structural change, deposit and degeneration	[redacted]	[redacted]
HLT: Cataract conditions	[redacted]	[redacted]
Cataract	[redacted]	[redacted]
	[redacted]	[redacted]
CARDIAC DISORDERS	[redacted]	[redacted]
HLGT: Cardiac arrhythmias	[redacted]	[redacted]
HLT: Cardiac conduction disorders	[redacted]	[redacted]
Atrioventricular block complete	[redacted]	[redacted]
Atrioventricular block second degree	[redacted]	[redacted]
HLT: Rate and rhythm disorders NEC	[redacted]	[redacted]
Arrhythmia	[redacted]	[redacted]
Tachycardia	[redacted]	[redacted]
HLT: Supraventricular arrhythmias	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]
Nodal rhythm	[redacted]	[redacted]
Sinus node dysfunction	[redacted]	[redacted]
Supraventricular tachycardia	[redacted]	[redacted]
HLT: Ventricular arrhythmias and cardiac arrest	[redacted]	[redacted]

PRIMARY SYSTEM ORGAN CLASS	Placebo	Dupilumab
Cardiac arrest	[redacted]	[redacted]
Ventricular arrhythmia	[redacted]	[redacted]
HLGT: Cardiac disorders, signs and symptoms NEC	[redacted]	[redacted]
HLT: Cardiac disorders NEC	[redacted]	[redacted]
Cardiovascular disorder	[redacted]	[redacted]
HLGT: Cardiac valve disorders	[redacted]	[redacted]
HLT: Mitral valvular disorders	[redacted]	[redacted]
Mitral valve incompetence	[redacted]	[redacted]
HLGT: Coronary artery disorders	[redacted]	[redacted]
HLT: Coronary artery disorders NEC	[redacted]	[redacted]
Coronary artery disease	[redacted]	[redacted]
HLT: Ischaemic coronary artery disorders	[redacted]	[redacted]
Acute coronary syndrome	[redacted]	[redacted]
Acute myocardial infarction	[redacted]	[redacted]
Angina pectoris	[redacted]	[redacted]
Angina unstable	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]
Myocardial ischaemia	[redacted]	[redacted]
Postinfarction angina	[redacted]	[redacted]
HLGT: Heart failures	[redacted]	[redacted]
HLT: Heart failures NEC	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]
Cardiac failure congestive	[redacted]	[redacted]
Cardiogenic shock	[redacted]	[redacted]
HLT: Right ventricular failures	[redacted]	[redacted]
Cor pulmonale	[redacted]	[redacted]
Cor pulmonale acute	[redacted]	[redacted]
	[redacted]	[redacted]
VASCULAR DISORDERS	[redacted]	[redacted]
HLGT: Arteriosclerosis, stenosis, vascular insufficiency and necrosis	[redacted]	[redacted]
HLT: Peripheral vasoconstriction, necrosis and vascular insufficiency	[redacted]	[redacted]
Extremity necrosis	[redacted]	[redacted]
Peripheral arterial occlusive disease	[redacted]	[redacted]
Peripheral artery occlusion	[redacted]	[redacted]
HLGT: Embolism and thrombosis	[redacted]	[redacted]
HLT: Peripheral embolism and thrombosis	[redacted]	[redacted]
Deep vein thrombosis	[redacted]	[redacted]
HLGT: Vascular disorders NEC	[redacted]	[redacted]
HLT: Peripheral vascular disorders NEC	[redacted]	[redacted]
Peripheral vascular disorder	[redacted]	[redacted]
HLGT: Vascular hypertensive disorders	[redacted]	[redacted]
HLT: Accelerated and malignant hypertension	[redacted]	[redacted]
Hypertensive crisis	[redacted]	[redacted]
Hypertensive emergency	[redacted]	[redacted]
	[redacted]	[redacted]

PRIMARY SYSTEM ORGAN CLASS	Placebo	Dupilumab
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	[redacted]	[redacted]
HLGT: Bronchial disorders (excl neoplasms)	[redacted]	[redacted]
HLT: Bronchospasm and obstruction	[redacted]	[redacted]
Bronchospasm	[redacted]	[redacted]
Chronic obstructive pulmonary disease	[redacted]	[redacted]
HLGT: Lower respiratory tract disorders (excl obstruction and infection)	[redacted]	[redacted]
HLT: Parenchymal lung disorders NEC	[redacted]	[redacted]
Atelectasis	[redacted]	[redacted]
HLT: Pulmonary oedemas	[redacted]	[redacted]
Acute pulmonary oedema	[redacted]	[redacted]
Acute respiratory distress syndrome	[redacted]	[redacted]
Pulmonary oedema	[redacted]	[redacted]
HLGT: Pleural disorders	[redacted]	[redacted]
HLT: Pleural infections and inflammations	[redacted]	[redacted]
Pleurisy	[redacted]	[redacted]
HLT: Pneumothorax and pleural effusions NEC	[redacted]	[redacted]
Hydrothorax	[redacted]	[redacted]
Pneumothorax	[redacted]	[redacted]
Pneumothorax spontaneous	[redacted]	[redacted]
HLGT: Respiratory disorders NEC	[redacted]	[redacted]
HLT: Conditions associated with abnormal gas exchange	[redacted]	[redacted]
Hypoxia	[redacted]	[redacted]
HLT: Respiratory failures (excl neonatal)	[redacted]	[redacted]
Acute respiratory failure	[redacted]	[redacted]
Chronic respiratory failure	[redacted]	[redacted]
Respiratory failure	[redacted]	[redacted]
	[redacted]	[redacted]
GASTROINTESTINAL DISORDERS	[redacted]	[redacted]
HLGT: Abdominal hernias and other abdominal wall conditions	[redacted]	[redacted]
HLT: Abdominal hernias NEC	[redacted]	[redacted]
Abdominal hernia	[redacted]	[redacted]
HLT: Umbilical hernias	[redacted]	[redacted]
Umbilical hernia	[redacted]	[redacted]
HLGT: Benign neoplasms gastrointestinal	[redacted]	[redacted]
HLT: Benign neoplasms gastrointestinal (excl oral cavity)	[redacted]	[redacted]
Intestinal polyp	[redacted]	[redacted]
HLGT: Exocrine pancreas conditions	[redacted]	[redacted]
HLT: Acute and chronic pancreatitis	[redacted]	[redacted]
Pancreatitis	[redacted]	[redacted]
Pancreatitis acute	[redacted]	[redacted]
HLGT: Gastrointestinal haemorrhages NEC	[redacted]	[redacted]
HLT: Intestinal haemorrhages	[redacted]	[redacted]
Rectal haemorrhage	[redacted]	[redacted]
HLT: Non-site specific gastrointestinal haemorrhages	[redacted]	[redacted]
Upper gastrointestinal haemorrhage	[redacted]	[redacted]

PRIMARY SYSTEM ORGAN CLASS	Placebo	Dupilumab
HLGT: Gastrointestinal inflammatory conditions	[redacted]	[redacted]
HLT: Colitis (excl infective)	[redacted]	[redacted]
Colitis	[redacted]	[redacted]
HLT: Gastritis (excl infective)	[redacted]	[redacted]
Gastritis	[redacted]	[redacted]
HLGT: Gastrointestinal signs and symptoms	[redacted]	[redacted]
HLT: Gastrointestinal and abdominal pains (excl oral and throat)	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
HLGT: Gastrointestinal stenosis and obstruction	[redacted]	[redacted]
HLT: Duodenal and small intestinal stenosis and obstruction	[redacted]	[redacted]
Small intestinal obstruction	[redacted]	[redacted]
HLT: Gastrointestinal stenosis and obstruction NEC	[redacted]	[redacted]
Subileus	[redacted]	[redacted]
HLT: Large intestinal stenosis and obstruction	[redacted]	[redacted]
Large intestinal stenosis	[redacted]	[redacted]
HLGT: Gastrointestinal vascular conditions	[redacted]	[redacted]
HLT: Gastrointestinal vascular occlusion and infarction	[redacted]	[redacted]
Intestinal ischaemia	[redacted]	[redacted]
	[redacted]	[redacted]
HEPATOBILIARY DISORDERS	[redacted]	[redacted]
HLGT: Bile duct disorders	[redacted]	[redacted]
HLT: Obstructive bile duct disorders (excl neoplasms)	[redacted]	[redacted]
Bile duct stone	[redacted]	[redacted]
HLGT: Gallbladder disorders	[redacted]	[redacted]
HLT: Cholecystitis and cholelithiasis	[redacted]	[redacted]
Cholecystitis	[redacted]	[redacted]
Cholecystitis acute	[redacted]	[redacted]
Cholelithiasis	[redacted]	[redacted]
HLGT: Hepatic and hepatobiliary disorders	[redacted]	[redacted]
HLT: Hepatic enzymes and function abnormalities	[redacted]	[redacted]
Hepatic function abnormal	[redacted]	[redacted]
HLT: Hepatic failure and associated disorders	[redacted]	[redacted]
Hepatic failure	[redacted]	[redacted]
Hepatorenal syndrome	[redacted]	[redacted]
	[redacted]	[redacted]
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	[redacted]	[redacted]
HLGT: Muscle disorders	[redacted]	[redacted]
HLT: Myopathies	[redacted]	[redacted]
Rhabdomyolysis	[redacted]	[redacted]
	[redacted]	[redacted]
RENAL AND URINARY DISORDERS	[redacted]	[redacted]
HLGT: Nephropathies	[redacted]	[redacted]
HLT: Glomerulonephritis and nephrotic syndrome	[redacted]	[redacted]
Glomerulonephritis	[redacted]	[redacted]
HLT: Nephritis NEC	[redacted]	[redacted]

PRIMARY SYSTEM ORGAN CLASS	Placebo	Dupilumab
Nephritis	[redacted]	[redacted]
HLGT: Renal disorders (excl nephropathies)	[redacted]	[redacted]
HLT: Renal failure and impairment	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]
Chronic kidney disease	[redacted]	[redacted]
Renal failure	[redacted]	[redacted]
HLGT: Urinary tract signs and symptoms	[redacted]	[redacted]
HLT: Urinary abnormalities	[redacted]	[redacted]
Haematuria	[redacted]	[redacted]
	[redacted]	[redacted]
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	[redacted]	[redacted]
HLGT: Ovarian and fallopian tube disorders	[redacted]	[redacted]
HLT: Ovarian and fallopian tube cysts and neoplasms	[redacted]	[redacted]
Ovarian cyst	[redacted]	[redacted]
HLGT: Prostatic disorders (excl infections and inflammations)	[redacted]	[redacted]
HLT: Prostatic neoplasms and hypertrophy	[redacted]	[redacted]
Benign prostatic hyperplasia	[redacted]	[redacted]
	[redacted]	[redacted]
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	[redacted]	[redacted]
HLGT: Body temperature conditions	[redacted]	[redacted]
HLT: Febrile disorders	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
HLGT: Fatal outcomes	[redacted]	[redacted]
HLT: Death and sudden death	[redacted]	[redacted]
Death	[redacted]	[redacted]
Sudden cardiac death	[redacted]	[redacted]
Sudden death	[redacted]	[redacted]
HLGT: General system disorders NEC	[redacted]	[redacted]
HLT: Pain and discomfort NEC	[redacted]	[redacted]
Chest pain	[redacted]	[redacted]
Non-cardiac chest pain	[redacted]	[redacted]
	[redacted]	[redacted]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	[redacted]	[redacted]
HLGT: Bone and joint injuries	[redacted]	[redacted]
HLT: Limb fractures and dislocations	[redacted]	[redacted]
Ankle fracture	[redacted]	[redacted]
Femoral neck fracture	[redacted]	[redacted]
Femur fracture	[redacted]	[redacted]
Fibula fracture	[redacted]	[redacted]
Tibia fracture	[redacted]	[redacted]
HLT: Spinal fractures and dislocations	[redacted]	[redacted]
Spinal compression fracture	[redacted]	[redacted]
HLT: Thoracic cage fractures and dislocations	[redacted]	[redacted]
Rib fracture	[redacted]	[redacted]
HLGT: Injuries NEC	[redacted]	[redacted]

PRIMARY SYSTEM ORGAN CLASS	Placebo	Dupilumab
HLT: Chest and respiratory tract injuries NEC	[redacted]	[redacted]
Pneumothorax traumatic	[redacted]	[redacted]
HLT: Non-site specific injuries NEC	[redacted]	[redacted]
Fall	[redacted]	[redacted]
Road traffic accident	[redacted]	[redacted]
HLT: Site specific injuries NEC	[redacted]	[redacted]
Head injury	[redacted]	[redacted]
HLT: Skin injuries NEC	[redacted]	[redacted]
Skin abrasion	[redacted]	[redacted]
HLGT: Injuries by physical agents	[redacted]	[redacted]
HLT: Thermal burns	[redacted]	[redacted]
Thermal burn	[redacted]	[redacted]

Appendix 4. Exacerbations rate calculations

Whittaker_Wallace_exacerbation rates.xlsm

References

1. Calverley PMA. Minimal Clinically Important Difference—Exacerbations of COPD. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2005;2(1):143-8.
2. Jones PW, Beeh KM, Chapman KR, Decramer M, Mahler DA, Wedzicha JA. Minimal clinically important differences in pharmacological trials. American journal of respiratory and critical care medicine. 2014;189(3):250-5.
3. Crim C, Frith LJ, Midwinter D, Donohue JF. FEV(1) Minimum Important Difference versus Minimal Detectable Difference? In Search of the Unicorn. Am J Respir Crit Care Med. 2021;203(12):1573-6.
4. Jones PW. St. George's Respiratory Questionnaire: MCID. COPD. 2005;2(1):75-9.
5. St George's University of London. Minimum Clinically Important Difference (MCID) 2024 [Available from: https://www.sgul.ac.uk/research/research-operations/research-administration/st-georges-respiratory-questionnaire/minimum-clinically-important-difference-mcid.
6. Jones PW, Gelhorn H, Wilson H, Karlsson N, Menjoge S, Müllerova H, et al. Responder analyses for treatment effects in COPD using the St George's Respiratory Questionnaire. Chronic Obstructive Pulmonary Diseases. 2017;4(2):124.
7. Medicine.com. Dupilumab 2020 [Available from: https://www.medicine.com/drug/dupilumab/hcp.
8. Anzueto A. Impact of exacerbations on COPD. Eur Respir Rev. 2010;19(116):113-8.
9. Leem AY, Park B, Kim YS, Chang J, Won S, Jung JY. Longitudinal decline in lung function: a community-based cohort study in Korea. Scientific reports. 2019;9(1):13614.
10. Ramos FL, Krahnke JS, Kim V. Clinical issues of mucus accumulation in COPD. Int J Chron Obstruct Pulmon Dis. 2014;9:139-50.
11. Newby C, Agbetile J, Hargadon B, Monteiro W, Green R, Pavord I, et al. Lung function decline and variable airway inflammatory pattern: longitudinal analysis of severe asthma. Journal of Allergy and Clinical Immunology. 2014;134(2):287-94. e5.
12. Castro M, Papi A, Porsbjerg C, Lugogo N, Brightling C, González-Barcala F-J, et al. Evaluating the Effect of Dupilumab on Type 2 Airway Inflammation and Mucus Plugging in Patients with Uncontrolled Moderate-To-Severe Asthma: the VESTIGE Trial. Journal of Allergy and Clinical Immunology. 2024;153(2):AB368.
13. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. New England journal of medicine. 2018;378(26):2486-96.
14. Whittaker H, Rothnie KJ, Quint JK. Cause-specific mortality in COPD subpopulations: a cohort study of 339 647 people in England. Thorax. 2024;79(3):202-8.
15. Wells JM, Criner GJ, Halpin DM, Han MK, Jain R, Lange P, et al. Mortality risk and serious cardiopulmonary events in moderate-to-severe COPD: post hoc analysis of the IMPACT trial. Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation. 2023;10(1):33.
16. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease https://goldcopd.org/2025-gold-report/. 2025.
17. Lee HW, Park J, Jo J, Jang EJ, Lee C-H. Comparisons of exacerbations and mortality among regular inhaled therapies for patients with stable chronic obstructive pulmonary disease: systematic review and Bayesian network meta-analysis. PLoS medicine. 2019;16(11):e1002958.
18. Leivseth L, Brumpton BM, Nilsen TIL, Mai X-M, Johnsen R, Langhammer A. GOLD classifications and mortality in chronic obstructive pulmonary disease: the HUNT Study, Norway. Thorax. 2013;68(10):914-21.
19. Shavelle RM, Paculdo DR, Kush SJ, Mannino DM, Strauss DJ. Life expectancy and years of life lost in chronic obstructive pulmonary disease: findings from the NHANES III Follow-up Study. Int J Chron Obstruct Pulmon Dis. 2009;4:137-48.
20. Whittaker H, Rubino A, Müllerová H, Morris T, Varghese P, Xu Y, et al. Frequency and Severity of Exacerbations of COPD Associated with Future Risk of Exacerbations and Mortality: A UK Routine Health Care Data Study. Int J Chron Obstruct Pulmon Dis. 2022;17:427-37.
21. Royal College of Physicians. National COPD Audit 2008 Steering Group, 2008. Report of The National Chronic Obstructive Pulmonary Disease Audit 2008: clinical audit of COPD exacerbations admitted to acute NHS units across the UK 2008 [Available from: https://www.rcp.ac.uk/media/0vhhctku/copd-clinical-report-november-2008.pdf.

22. National Institute for Health and Care Excellence. Single Technology Appraisal: Roflumilast for treating chronic obstructive pulmonary disease (review of technology appraisal guidance 244) [ID984]; Committee Papers [Available from: https://www.nice.org.uk/guidance/ta461/documents/committee-papers.
23. Royal College of Physicians. National Asthma and Chronic Obstructive Pulmonary Disease Audit Programme (NACAP) Clinical Outcomes October 2018-March 2020 Summary Report. 2023 March 2023.
24. Hartl S, Lopez-Campos JL, Pozo-Rodriguez F, Castro-Acosta A, Studnicka M, Kaiser B, Roberts CM. Risk of death and readmission of hospital-admitted COPD exacerbations: European COPD Audit. Eur Respir J. 2016;47(1):113-21.
25. Rabe KF, Martinez FJ, Ferguson GT, Wang C, Singh D, Wedzicha JA, et al. Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate-to-Very-Severe COPD. N Engl J Med. 2020;383(1):35-48.
26. National Institute for Health and Care Excellence. Chronic obstructive pulmonary disease in over 16s: diagnosis and management. Economic model report (NICE guideline NG115). 2018.
27. Spencer M, Briggs AH, Grossman RF, Rance L. Development of an economic model to assess the cost effectiveness of treatment interventions for chronic obstructive pulmonary disease. Pharmacoeconomics. 2005;23(6):619-37.
28. Rutten-van Molken M, Lee TA. Economic modeling in chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2006;3(7):630-4.
29. Borg S, Ericsson A, Wedzicha J, Gulsvik A, Lundback B, Donaldson GC, Sullivan SD. A computer simulation model of the natural history and economic impact of chronic obstructive pulmonary disease. Value Health. 2004;7(2):153-67.
30. Sadatsafavi M, Ghanbarian S, Adibi A, Johnson K, FitzGerald JM, Flanagan W, et al. Development and validation of the Evaluation Platform in COPD (EPIC): a population-based outcomes model of COPD for Canada. Med Decis Making. 2019;39(2):152-67.
31. Graul EL, Nordon C, Rhodes K, Marshall J, Menon S, Kallis C, et al. Temporal Risk of Nonfatal Cardiovascular Events After Chronic Obstructive Pulmonary Disease Exacerbation: A Population-based Study. American Journal of Respiratory and Critical Care Medicine. 2024;209(8):960-72.
32. Mansur AH, Gonem S, Brown T, Burhan H, Chaudhuri R, Dodd JW, et al. Biologic therapy practices in severe asthma; outcomes from the UK Severe Asthma Registry and survey of specialist opinion. Clinical & Experimental Allergy. 2023;53(2):173-85.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Dupilumab for treating moderate to severe chronic obstructive pulmonary disease ID6235

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Asthma + Lung UK Taskforce for Lung Health
3. Job title or position	Policy Officer + Policy Manager
4a. Brief description of the organisation (including who funds it). How many members does it have?	Asthma + Lung UK is the nation's lung health charity representing all people across the UK living with a lung condition. Asthma + Lung UK provide the secretariat to the Taskforce for Lung Health. The Taskforce is a coalition of 52 members, including patients, carers, healthcare professionals, the voluntary sector, and professional associations. An Industries Forum, which works alongside the Taskforce, include representatives from the pharmaceutical, diagnostics, devices, and digital industries. The Taskforce for Lung Health receives grants from some members of the Industries Forum. The Industries Forum has no editorial control over the Taskforce.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Sanofi has provided £55,000 in grant funding toward the Taskforce for Lung Health. The Taskforce is funded by its Industries Forum. Sanofi provided £75,000 + VAT toward its COPD Medical Education Roadshow in collaboration with Asthma + Lung UK. Asthma + Lung UK co-branded this initiative and its policy team members presented to local HCPs across the UK during the roadshow, to inspire HCPs to engage with and influence their local policymakers to improve COPD care in their area. AstraZeneca provided £55,000 in grant funding toward the Taskforce for Lung Health. GSK provided £55,000 in grant funding toward the Taskforce for Lung Health. Verona Pharma provided £5,000 in grant funding toward the Taskforce for Lung Health. The Industries Forum has no editorial control over the Taskforce.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

5. How did you gather information about the experiences of patients and carers to include in your submission?	This submission includes patient testimony which was gathered by discussing these consultation questions in a COPD support A+LUK support group. We also posted a survey on A+LUK's Health Unlocked Forum. In total 16 patients responded to this survey. This submission also cites Asthma + Lung UK's annual 'Life with a Lung Condition' survey. This survey was open from January to March 2024 and received 10,436 responses across England.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	"I am breathless every time I do anything, even, for example, walking from the living room to the kitchen, a journey of only a few yards. After going upstairs, it takes me several minutes to get my breath back. The inability to perform even basic physical functions causes me considerable stress and, at times depression. My wife is my carer and does almost everything for me. This also, of course, causes me some stress as I feel as though I am just a burden." - Alan, a patient living with COPD. "I experience breathlessness daily, impacting my ability to do routine tasks. Many times, my breathlessness means I can't leave the house. I find the symptoms of COPD scary at times, particularly during the winter. In winter, my symptoms are much worse, and I find myself shorter of breath than usual*."* - Doreen, a patient living with COPD. The quotes, from patients from the COPD support group, demonstrate how COPD and the resulting breathlessness profoundly impact patients' lives and their families. Patients with COPD suffer from a range of symptoms, including breathlessness, cough and sputum production, poor sleep, depression, and skeletal muscle loss—such symptom burden can significantly impact people living with COPD's quality of life. A+LUK's 'Life with a Lung Condition' 2024 survey reveals the considerable impact of this disease on families.[1] 33% of COPD patients reported that their breathlessness 'often' or 'very often' impacts their ability to carry out family responsibilities.[2] Due to the debilitating symptoms of COPD, in many instances, family members have to act as carers. We hear from patients every day that they feel like a burden to their families, as their breathlessness leads to them needing help to carry out everyday tasks.

	"I feel very limited in the things I can do now, and I have become very anxious when I am in public in case, I get an episode of shortness of breath. I am tired and without energy much of the time and must rest frequently." - Lily, a patient living with COPD. Many patients with COPD have told us that it can be an isolating disease. It can have devastating consequences on general wellbeing with patients feeling hopeless, lonely, and scared. People with COPD are three times more likely to experience loneliness and social isolation than people without COPD.[3] In this year's 'Life with a Lung Condition' survey, 29% of COPD patients believe that their breathlessness 'often' or 'very often' prevents them from seeing their friends.[4] Patients tell us they often feel too anxious to leave the house, due to the fear of having an exacerbation in public. Anxiety and depression are common comorbidities in patients with COPD, with over one in three patients with COPD reporting symptoms of depression and anxiety.[5] Symptoms of COPD are a significant barrier to patients remaining active and participating in hobbies they used to enjoy. 38% of COPD patients reported in A+LUK's survey that their breathlessness 'often' or 'very often' impacts their ability to do their hobbies.[6] 55% of patients believed their breathlessness affected their ability to exercise,[7] demonstrating how patients face a life that is compromised through restricted activities. "I find the symptoms of COPD challenging and restricting. I cannot move as quickly up steps and hills. This restricts my activities in work, leisure, and socially." - David- a patient living with COPD. Patients tell us that due to their COPD symptoms, they have been forced to give up work. 44% of COPD patients are below retirement age, and around one-quarter are not in work due to their COPD.[8] COPD patients, who are in employment, report having to take more time off and that their breathlessness inhibits their performance at work. This year's 'Life with a Lung Condition' survey revealed that 42% of COPD patients in England believe that their breathlessness 'often' or 'very often' impacts their ability to work.[9] 11% of respondents with COPD reported having to reduce their working hours, due to their COPD, while 18% reported that they had to take sick leave due to their lung condition.[10] Every year COPD causes reductions in productivity due to illness and premature death, totalling £1.7 billion annually in England.[11]

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	"I worry about the side effects of steroid inhalers. I used to love to sing. However, now I can't sing, as I suffer from a dry mouth. When I broke my arm, I was diagnosed with osteopenia. My rheumatology consultant told me I had developed osteopenia, due to taking my high-dose steroid inhaler. They advise me to stop any form of steroid medication, but I have to take a steroid inhaler to manage my breathlessness." - Felicity, a patient with COPD and patient representative on the Taskforce. Most COPD patients are prescribed an inhaled corticosteroid (ICS) in combination with a bronchodilator. We have heard from patients that they are worried about the side effects of taking high-dose ICS inhalers, with one COPD patient who responded to the survey on the Health Unlocked Forum, suggesting that "without certain medication, my life would be very different now. However, I wish my steroid inhaler didn't have so many side effects." Another patient echoed these concerns telling us that "taking too much of my steroid inhaler brings excruciating leg cramps at night, but what choice do I have." Patients taking high-dose ICS inhalers are at a higher risk of increased side effects, especially oral candidiasis, dysphonia, pneumonia, and osteoporosis. Long-term ICS use is associated with a 52% increase in the likelihood of developing osteoporosis, so many patients like Felicity (as highlighted above) will suffer from bone density loss.[12] Many patients are not confident in the current treatments available, with one patient expressing that "the treatment that I'm on for my COPD doesn't feel to be particularly effective and every day I struggle with breathlessness." Another patient who responded to the Health Unlocked Forum survey said: "To be honest I think my current meds are just like a plaster on a limp amputation." Others also questioned the effectiveness of their current treatments, "I hardly use my bronchodilator inhaler as it doesn't seem to do anything."
8. Is there an unmet need for patients with this condition?	The current therapeutic approach does not meet all the needs of patients with COPD, and for many patients, the available treatments fail to decisively influence the course of the disease.[13] We have heard from patients, who take ICS and bronchodilator inhalers, that they are trapped in a vicious cycle of exacerbations and lung function decline. For these patients there is a huge unmet need and dupilumab could be potentially life-changing.

People with COPD still struggle to access their essential basic care. A+LUK's 'Living with a Lung Condition' survey revealed that there is huge unmet need for COPD patients and that only 10% of COPD patients in England reported receiving the 5 fundamentals of COPD care (smoking cessation, vaccination, pulmonary rehabilitation, personalised self-management plan, and optimising treatment for co-morbidities). [14]

Only 56% of COPD patients in this annual survey reported being offered stop-smoking cessation support and treatment, a critical intervention to stop the progression of this disease.[15] While only 33% of COPD patients surveyed responded that they have a self-management plan.[16] Self-management plans play a valuable role in supporting people with COPD to manage their condition and respond appropriately to changing symptoms. We are therefore concerned that the majority of COPD patients are not adequately supported to take control of their condition and manage their symptoms.

> "I would like to complete a course in pulmonary rehabilitation, as I believe it would help me to manage my symptoms. However, I know in my area there are long waiting lists." - Felicity, a patient living with COPD and a patient representative on the Taskforce.

We know that too few COPD patients have access to pulmonary rehabilitation (PR). PR is one of the most cost-effective interventions for COPD, with patients who have completed a course of PR being less likely to be admitted to hospital. The National COPD Audit found that 76% of people who completed a PR programme avoided hospital admission within six months after their initial assessment, compared to 62.1% who did not.[17] PR also reduces the length of hospital stay, with people who were admitted to hospital and had completed a PR course spending only 4.8 days in hospital in six months compared with 9.6 days for those who did not complete the programme.[18]

Despite the effectiveness of PR, just 32% of COPD patients in ALUK's survey reported that they have been offered a course of PR.[19] Inadequate capacity of PR services in many areas means that once patients are referred many will sit on a waiting list. Therefore, only 4.3% of the COPD population has completed a course of PR, demonstrating the huge unmet need for patients with COPD.[20]

Introducing new drugs to the treatment pathway for COPD patients could be transformative for some patients, but a huge amount of the unmet need of these patients, as the health system is failing to deliver the basic care

	these patients need and deserve. Only when basic care needs being met, and care optimised, can the rest of the unmet need be met by the introduction of new medication.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	"This new treatment gives me hope that in the future COPD patients will be able to have more effective treatments, which will give us a better quality of life and reduce the use of high-dose inhalers." - Alan, a patient living with COPD. Patients living with COPD have told us that dupilumab makes them hopeful that they will have a "better life quality and will be able to manage this disease." Another patient, who completed the survey on the Health Unlocked Forum survey, told us they think biologics will "help reduce terrible breathlessness, making walking and doing everyday tasks easier." Patients have also told us they think an advantage of dupilumab is that they could be able to reduce their steroid dose, potentially leading to a reduction in adverse side effects. One patient, who responded to the Health Unlocked Form survey, suggested that "a biologic might reduce the amount of steroid I have to use daily or am additionally need should I have an exacerbation or lung infection, which would help with reducing the unpleasant side effects I suffer with every day." Another patient echoed this, telling us that this new drug could allow them to "reduce the frequency I have to take my steroid inhaler, which damages my teeth and gums." This patient highlighted unlike their steroid inhaler; biologics will not leave an unpleasant residue in their mouth. A patient in the Health Unlocked Forum survey highlighted a potential advantage of biologics could be "easier to take, as you only have an injection once a month. "Another patient noted that "for me, it would potentially be fantastic as I believe biologics can also help with skin conditions."

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Patients have told us a potential disadvantage of dupilumab is that they may need to attend more hospital appointments. One respondent to the survey on the Health Unlocked Form stated that "the need for a further regular appointment for administration is quite restricting." Some patients also expressed that they are worried about the financial costs of attending the hospital once a month for the administration of a biologic – a sufficiently designed inclusive patient pathway would negate this concern, and key lessons on patient accessibility, such as home administration, should be learnt from the severe asthma biologics pathway and the AAC Consensus pathway work. In addition, patients have also highlighted the potential side effects of this new medicine, including rhinitis, joint pain and headaches. One patient told us that "the only disadvantage would be the worry about side effects, I read online that dupilumab can cause headaches. I already suffer from headaches, so I would be worried that taking it would make them worse."

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Dupilumab could be particularly beneficial for patients with a type 2 inflammation with a high eosinophil count of 300 cells per microliter or higher, as in clinical trials dupilumab was associated with fewer moderate or severe acute by 30% exacerbations than patients given the placebo.[21] Therefore, this treatment has the potential to improve the quality of life for many people with type 2 inflammation and help manage them this progressive and debilitating condition.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	People from the poorest 10% of households are more than two and a half times more likely to have COPD than someone from the most affluent 10% of households.[22] Poorer people with COPD have more exacerbations and the poorest people with COPD are being left further behind in terms of the care that they are receiving. [23] Therefore, dupilumab has the potential to address health inequalities, by improving outcomes and quality of life for COPD patients from most the deprived households.

Other issues

13. Are there any other issues that you would like the committee to consider?	The average age when people are diagnosed with COPD in the UK is 67 years old and it rarely affects patients under 40 years old.[24] Home administration of biologics for severe asthma patients has worked well, reducing geographical barriers to access. COPD patients are generally older, therefore it will be important to consider that some may have dexterity limitations and struggle to self-administer injections at home. 86% of people with COPD have at least one or more comorbidities.[25] At the time of diagnosis, the most prevalent comorbidities are mood and anxiety disorders (25.2% for patients with COPD vs 13.1% for patients who do not have COPD).[26] 15.6% of patients when they received their COPD diagnosis had diabetes, 15.5% had peripheral arterial disease and 13.3% had heart failure.[27] The presence of comorbid conditions has important consequences for disease assessment and management. Therefore, the committee must fully consider the interaction between this new treatment and comorbidities.

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[1] Asthma + Lung UK, *Life with a Lung Condition Survey* (2024). Data is available on request.
[2] Asthma + Lung UK, *Life with a Lung Condition Survey* (2024). Data is available on request.
[3] Suen A., Cenzer I. et al, National prevalence and risk factors for loneliness and social isolation among adults with chronic obstructive pulmonary disease, Journal of Pain and Symptom Management (2023). Accessed here.
[4] Asthma + Lung UK, *Life with a Lung Condition Survey* (2024). Data is available on request.
[5] Volpato, E., Peters, J., et al, *Nonpharmacological management of psychological distress in people living with COPD*, European Respiratory Review (2023). Accessed here.
[6] Asthma + Lung UK, *Life with a Lung Condition Survey* (2024). Data is available on request.
[7] Asthma + Lung UK, *Life with a Lung Condition Survey* (2024). Data is available on request.
[8] Adab P, Jordan RE, Fitzmaurice D, et al, Case-finding and improving patient outcomes for chronic obstructive pulmonary disease in primary care: the BLISS research programme including cluster RCT Southampton (UK), NIHR Journals Library (2021). Accessed here.
[9] Asthma + Lung UK, *Life with a Lung Condition Survey* (2024). Data is available on request.
[10] Asthma + Lung UK, *Life with a Lung Condition Survey* (2024). Data is available on request.
[11] A+LUK and Taskforce for Lung Health, *Saving your Breath: Technical Report,* (2023) Accessed here.
[12] Janson, C., Lisspers K., *et al, Osteoporosis and fracture risk associated with inhaled corticosteroid use among Swedish COPD patients: the ARCTIC study* European Respiratory Journal (2021).Accessed here
*13*Rosenwasser, Y., Berger, R. and Loewy, Z., *Therapeutic approaches for Chronic Obstructive Pulmonary,*(2022) Accessed here.
[14] Asthma + Lung UK, *Life with a Lung Condition Survey* (2024). Data is available on request.
[15] Asthma + Lung UK, *Life with a Lung Condition Survey* (2024). Data is available on request.
[16] Asthma + Lung UK, *Life with a Lung Condition Survey* (2024). Data is available on request.
[17] National COPD Audit Programme, Pulmonary Rehabilitation: Beyond Breathing Better, (2018) Accessed here.
[18] National COPD Audit Programme, Pulmonary Rehabilitation: Beyond Breathing Better, (2018) Accessed here.
[19] Asthma + Lung UK, *Life with a Lung Condition Survey* (2024). Data is available on request.

[20] Asthma and Lung UK. *Investing in Breath: Measuring the economic cost of asthma and COPD in the UK and identifying ways to reduce it through better diagnosis and care* (2023) Accessed here.
[21] Bhatt, P., Kalus, F. and et al, *Dupliumab for COPD with Type* 2 Inflammation Indicated by Eosinophil counts, The New England Medicine Journal (2023) Accessed here.
[22] Asthma + Lung UK, *COPD in the UK: Delayed diagnosis and unequal care* (2022) Accessed here.
[23] *British Lung Foundation. 2021. Failing on the fundamentals: Insights from those living with chronic obstructive pulmonary disease (COPD) around the UK. British Lung Foundation. Accessed here (October 2022). PP. 14-15.*
24 Devereux G. ABC of chronic obstructive pulmonary disease: definition, epidemiology, and risk factors. BMJ *(*2006). Accessed here.
[25] Skajaa N., Laugesen, K., et al, Comorbidities and mortality among patients with COPD, BMJ Open Respiratory Research (2023). Accessed here.
[26] Skajaa N., Laugesen, K., et al, Comorbidities and mortality among patients with COPD, BMJ Open Respiratory Research (2023). Accessed here.
[27] Skajaa N., Laugesen, K., et al, Comorbidities and mortality among patients with COPD, BMJ Open Respiratory Research (2023). Accessed here.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Dupilumab for treating moderate to severe chronic obstructive pulmonary disease [ID6235]

Clinical expert statement

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Clinical expert statement

Dupilumab for treating moderate to severe chronic obstructive pulmonary disease [ID6235]

NICE National Institute for Health and Care Excellence

Part 1: Treating moderate to severe COPD and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Grainne d'Ancona
2. Name of organisation	Guy's and St Thomas' NHS Foundation Trust
3. Job title or position	Consultant Pharmacist, respiratory medicine
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with COPD? ☒ A specialist in the clinical evidence base for COPD or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for moderate to severe COPD? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	1. stop progression of the disease (that is arrest the accelerated lung function decline – FEV_1), 2. minimise exposure to oral corticosteroids (OCS, that is a moderate exacerbation frequency)

	3. reduce unscheduled care eg ED presentation or hospital admission (that is severe exacerbation frequency) 4. reduce the impact of COPD on people's lives (the COPD Assessment Test CAT scores range from 0-40, where higher scores indicate a greater impact) 5. maintain personal independence wrt exercise, ADLs, 6. reduce premature mortality
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Using the persons baseline values for 1-4 above: 1. FEV_1 reflect natural decline over time 2. A reduction in OCS (courses per year or maintenance OCS dose) of 50% 3. A reduction of 50% 4. A reduction of $\geq$2 points in the CAT score (the minimum clinically important difference is 2 points).
10. In your view, is there an unmet need for patients and healthcare professionals in moderate to severe COPD?	Definitely.
11. How is moderate to severe COPD currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Current management involves a combination of optimised inhaler therapy (dual bronchodilation or triple therapy) and other high value often non-pharmacological interventions: pulmonary rehabilitation, tobacco dependence support and vaccination. Most pathways are based on a combination of GOLD recommendations and NICE guidance. Practice is slowly merging particularly around the place of triple therapy and moving from single to dual bronchodilation. I hope biologics will not only transform outcomes in this group, but raise the standards of "basic" care by establishing what optimisation looks like (eg to be eligible for a biologic)
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Lessons can be learned from how biologics are used in severe asthma, but their newness with changes in NHSE and commissioning will demand a different way of working.

• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The drug acquisition cost appears high compared to current therapies (eg inhalers), but the value proposition needs to be clear to avoid decisions not to treat (in a financially challenged environment). I think the decision to initiation treatment should be by a specialist MDT, but the process for prescribing, supply and administration could be outside hospital. This could be via home care or primary care providers, it doesn't need to be secondary/tertiary care delivered.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes! I am excited to use biologics to improve the outcomes and lives of people with COPD.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	I don't think the optimal group to use these agents in (for maximal benefit) is clear. A programme of real world evaluation is essential to support this.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	The nature of them being a refrigerated injection will make them more difficult to manage than inhalers.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	I think it is essential that the purpose of the biologic is clarified at the beginning to establish what success looks like for that individual. This will encourage appropriate review and ongoing optimisation.

17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Potentially prolong people staying in work (given the cohort age).
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes, this has the potential to be truly transformative
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	So far, the side effect profile raises no concerns. A post-marketing surveillance will be in place
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Mostly, yes – a wide range of patients were included (smokers/not, eos counts >0.3 and <0.3) etc. Our patients are unlikely to agree to significant numbers of follow up appointments (particularly if in hospital), so post-initiation care would need to reflect this and potentially use digital innovations like remote monitoring and virtual review.

21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance 461 [TA461]?	No. Very little roflumilast used in practice
23. How do data on real-world experience compare with the trial data?	Minimal RWE available currently
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people.	Appropriate access to this treatment is likely to reduce the health inequalities experienced by those with COPD living in deprived areas or those where COPD management has not been prioritised (eg long waits for PR or a disorganised smoking cessation service)

Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

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Single Technology Appraisal

Dupilumab for treating moderate to severe chronic obstructive pulmonary disease [ID6235]

Clinical expert statement

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NICE National Institute for Health and Care Excellence

Part 1: Treating moderate to severe COPD and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Richard Russell
2. Name of organisation	King's College London, King's Centre for Lung Health
3. Job title or position	Head of Dept Peter Gorer Dept of Immunobiology and Clinical Reader in Respiratory Medicine, Chair of British Thoracic Society
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with COPD? ☒ A specialist in the clinical evidence base for COPD or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nothing to declare
8. What is the main aim of treatment for moderate to severe COPD? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	1.To reduce risk of moderate or severe exacerbations (Attacks/Flares) of disease. 2. To improve symptoms and thus quality of life 3. To further reduce risk of disease progression and thus premature death

	4. To prevent harm from the oral corticosteroid burden.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A reduction of anything up to 20% reduction in risk of exacerbation. For lung function (e.g. forced expiratory volume in 1 second) as there is little association between this and symptom of breathlessness this outcome has little meaning.
10. In your view, is there an unmet need for patients and healthcare professionals in moderate to severe COPD?	Yes. There are significant unmet needs for these patients. From the patient perspective (please see the Patient Voices report submitted to NICE) there are significant unmet needs. These apply across all severities of COPD. The unmet needs are: inadequate treatments to prevent exacerbations of COPD; ineffective treatments of exacerbations of COPD (a >40% treatment failure rate at 90days); inadequate treatments to improve lung function and quality of life for moderate to severe COPD patients; inequitable and variable access to fundamental therapies for moderate to severe COPD across the UK; lack of connected provision of both healthcare and information for patients. This disease leads to a huge burden in all healthcare settings, often with a focus on winter bed pressures and secondary care admissions. This often ignores the burden on both individual patients as well as their carers and families and the whole societal impact that occurs. Exacerbations themselves have been demonstrated to have effects on co-morbid conditions which has a multiplier effect on their impact. This is especially relevant to cardiovascular disease (the largest cause of death in UK) with a greater than doubling of risk of significant major adverse cardiac event after an exacerbation. All lead to increase pre-mature mortality but with a significant time of increased symptoms, morbidity and healthcare utilisation. The burden of COPD and COPD exacerbations to the UK is enormous. The cost of COPD is over 2 billion GPB a year with over 1 billion being spent on exacerbations. There is one exacerbation consultation every 20seconds in the Uk and one death every 20 minutes. The UK has one of the worst outcomes for COPD mortality in the world.
11. How is moderate to severe COPD currently treated in the NHS?	There is national guidance for the management of COPD which was produced by NICE (NG115, 2010 short update2018) which is used as the template for local (ICS level) guidelines such as the Hampshire Isle of Wight COPD (ref) guideline.

• Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Attention is also paid to the Global Obstructive Lung Disease Strategy (Gold, www.gold.org) which has the global status as the most up to date treatment recommendations. This is evidence based and updated every year. The pathway of care is well defined but poorly applied and implemented. This is in part due to a pervasive nihilism throughout the healthcare community towards COPD and a perception of the futility of treatment. There is also an unconscious bias towards smokers and ex-smokers with disease which also affects the patients' own perceptions. The fundamentals of care are well defined, well evidenced and simple as per evidence submitted in the Patient Voice report. But they are not easy to implement due to a lack of focus and integration across all healthcare settings. There is a need for a clarity of priority and purpose. I have worked driving change for NHSE and ICS's and in other healthcare systems across the world. The challenges are the same in every country and area. The necessary interventions/actions are the same. But the implementation/solution finding will be variable. At the pathway level it is about "what we should do" rather than "how to do it". The new technology is a potential game changer for COPD both in its direct use but also in changing the paradigm and negativity for COPD patients. The "Patient Voice" piece demonstrates the urgent need for this transformation of care provision for patients. This technology provides an opportunity that will enable a new way of thinking as well as providing a direct opportunity for a new therapy for some. I believe that we need to use the potential for biologic therapy to leverage change into a more "cardiological" pro-active and optimisation approach. Moving away from a stepwise flow approach into a "pillars" of care approach of fundamental interventions which embeds highly effective management as the foundations to build on. Then the potential for some patients to be identified who will benefit from the new technology will drive the fundamentals as well as enabling other "advanced" therapies. Driving care by enabling HCP's to ask the right and critical questions and in doing so they will optimise the care for those living with COPD. Our patients have demanded that

	we do better in this way from the point of presentation through to the discussion and consideration of treatment options.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	• This new therapy is different in several critical ways: 1. Efficacy is driven by a simply identified specific and precise biologic phenotype which predicts both risk and response. 2. It is an injectable, which solves the significant issues with both adherence and ability to use inhaled therapies in COPD. 3. As a therapy for patients, all treatment decisions can be made in a remote manner and treatment given in a close to home setting (home care) reducing the need and risk of travel. 4. By effectively preventing the effect of one phenotype of exacerbation (eosinophilic) this also enables a focus on the other types which exist to further improve care. 5. It is effective without clear risks of treatment (in comparison with oral corticosteroids) which will reassure patients as well as reduce the significant morbidity and costs which therapies carry. • This new therapy can be instigated and given in a close to home setting. There is no reason why this cannot be in the patient's home. This already occurs in Dermatology, Rheumatology and Gastroenterology with similar treatments. This is essential for patients with COPD who find travel problematic and a significant barrier to accessing healthcare. This forms part of the inequity of care that we see across England for patients with COPD. • The main investment is in the funding of the therapy and then the intellectual and emotional investment in prioritising COPD as an urgent and essential healthcare need. The fundamentals of care are what we should be doing and can do already. The provision of this new therapy can be supported by the manufacturers. There is a need for governance and data collection that can inform the use, efficacy and safety of this new therapy in a real-world setting. This needs to be seen as an opportunity to provide an essential resource as well as inform commissioners and central planners as to the care of patients with COPD. Ideally this should take the form of a register for those treated

	with biologics for COPD (which will be funded by the manufacturers) and supported by the British Thoracic Society and hosted by a UK academic centre. The data acquisition will be performed as part of clinical review and will be part of the standard pre-requisite for prescription. This will be at ICS level and will enable local commissioners to "know" their own data and inform future planning. The ICS respiratory networks (in existence since 2019) are ideally placed to lead this implementation.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes. • This new treatment has been demonstrated in two large global RCT's to provide significant clinical improvements in COPD patients who were optimised according to current care. In reducing exacerbations this will reduce the burden of COPD in many respects because of exacerbations: loss of lung function, disease progression, hospital admission, need for treatment and thus reduction in treatment related side effects, reduction in cardiovascular impact and thus an increase in length of life/reduction in premature death. • This will increase Houl in ADDITION to current care and not in comparison with it. This is an additional therapy that will added to the benefit of optimal care as per the RCT.
14. Are there any groups of people for whom the technology would be effective (or appropriate) than the general population?	This therapy should and will be targeted at those with the appropriate phenotype (blood eosinophils >300 cells/microlitre, measured in a controlled state i.e. not on oral steroids) who are taking inhaled triple therapy who are at an increased risk of future exacerbation predicted by previous exacerbation (moderate or severe). It is unlikely to be effective if blood eosinophils are <100 cells/microlitre. It is also unknown what the effect size may be on patients in between these values although other therapeutic effects that are seen with other therapies with increased efficacy in the eosinophilic phenotype suggest that they will respond, and the degree of response will depend upon their individual underlying risk of exacerbation. This is mostly drive by previous exacerbation history as well as increased cough with sputum production and disease severity.

15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	This treatment will be easier to use as there is a clearly defined phenotype which is readily identified and the treatment is a simple injectable thus is easier to give and teach how to give than standard inhalers.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	This therapy should be considered only in those patients with eosinophils >300 cells per microlitre and a history of two exacerbations in the year prior to treatment. There are should be no pre-defined stop criteria as although the underpinning biology of the eosinophilic phenotype has been treated there is NO evidence that this factor is changed. COPD exacerbations are seasonal making short term assessments of efficacy hard and it is reasonable to recommend a 2 year treatment window in order to assess patients while allowing for the variability of the incidence of exacerbations.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Yes. This therapy will result in: • A reduction in health inequality via improved access to effective care for all. • Improvement in patients quality of life as treatment will be given in the home environment, this may also reduce cost through a reduction in health care related attendances. • To treat there will be a focus on the needs of the induvial with COPD that will result in a more holistic assessment and appropriate provision of care and information. • There will be a reduction in carer burden via an improvement in clinical outcomes. E.g. in the “Patient voice” Report 1/3 of carers were aged between 18-35 years old and 50% of these were caring for their family members with COPD for >50hours a week. This data leads to an estimate of the total cost to society as a whole of COPD for this young group of approximately 25million hours a week spent caring for COPD in a younger

	working age population. The estimated cost to economy is approximately 375 million pounds a week in lost income a week at 15/hr.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any unmet need of the patient population?	Yes • Patients with moderate to severe COPD still exacerbate on optimal inhaled treatment. 30% of COPD patients have Eos.> 300 cells per microliter, these patients have 4 exacerbations a year (data from the ABRA study , Lancet Respir Med. 2025 Jan;13(1):59-68. doi: 10.1016/S2213-2600(24)00299-6.). This new therapy will be a step change for these patients. • COPD patients have significant health inequity and inequality with increased burden of morbidity and mortality. This new therapy will address this burden as it will enable better access to care and not discriminate against those from more deprived areas who tend to smoke more. Treatment at home will reduce the cost of travel and thus obtaining healthcare for more deprived populations.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	This new therapy has a demonstrated safe adverse event profile.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes • N/A • The most important outcome from the clinical trials was the exacerbation rate as measured prospectively in the trial • N/A • No
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance 461 [TA461]?	No
23. How do data on real-world experience compare with the trial data?	N/A
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be considered when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme.	Inequality is a significant problem for patients with COPD. They tend to be from more deprived areas. They find accessing healthcare difficult both practically and as related to cost. Deprived areas have an increased prevalence of smoking which results in an inbuilt bias and inequity of health care provision. This treatment may lead to an improvement in the economic and health status of carers. Ethnic minorities are under-represented in populations diagnosed and treated for COPD. This new therapy will enable a diagnosis and care to be provided near to home and not in a distant healthcare setting that results in reduced access to care for these groups. • Both smokers and Ex smokers were recruited into the studies of this new treatment with equal efficacy for both. • Smoking leads to more exacerbations and thus it is possible that they may benefit more from this therapy due to this increased risk • No • Yes, if access is not practicable and restricted then disabled patients with COPD will not be treated. Care close to or in the home setting will reduce this risk.

Find more general information about the Equality Act and equalities issues here.	

NICE National Institute for Health and Care Excellence

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

1. Exacerbations of COPD cause a burden for COPD patients, healthcare professionals, healthcare systems and society.
2. COPD patients of all severity and on current best practice are at risk of exacerbations.
3. Dupilumab in COPD patients with a specific phenotype of inflammation will reduce the rate of exacerbations.
4. Dupilumab will enable improvements in COPD care to occur and reduce the current therapeutic nihilism.
5. Dupilumab can be provided in a “care at home” setting and initiated without placing a burden on patients thus reducing the inbuilt health inequalities that exist for COPD patients.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Dupilumab for treating moderate to severe chronic obstructive pulmonary disease [ID6235]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with chronic obstructive pulmonary disease (COPD) or caring for a patient with COPD. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

NICE National Institute for Health and Care Excellence

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Monday 24 March 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

Part 1: Living with this condition or caring for a patient with COPD

Table 1 About you, COPD, current treatments and equality

1. Your name	
2. Are you (please tick all that apply)	☒ A patient with COPD? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with COPD? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Asthma & Lung UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with COPD? **If you are a carer (for someone with COPD) please share your experience of caring for them**	I was diagnosed with Chronic Obstructive Pulmonary Disease (COPD) in 2010 when I was 52 years old. Before I lived an active life, I worked as a window cleaner, and in my free time, I coached my local youth football team and went to Leicester City football matches with my son. My COPD has now progressed to the point where I am reliant on an oxygen machine and often find it difficult to leave the house. Despite being on triple therapy, my lung function is only 35%. Every day I am on oxygen for 16 hours a day, 8 litres when I am moving and 1-2 litres when I am sedentary. Leaving the house is difficult, as my oxygen only lasts an hour. My life is disrupted by exacerbations and hospital admissions, causing me and my family a lot of fear and anxiety. Most days I cough up blood, which my wife finds very distressing. Last year I was hospitalised twice for between 4-10 days and had 11 exacerbations. COPD and the resulting breathlessness have significantly impacted my quality of life. I had to give up work and many of my hobbies. Anytime I move my oxygen levels plummet, and I struggle to go up the stairs and perform basic tasks at home, such as cooking and hoovering. Therefore, I rely on my wife and children to help me with everyday tasks. Like many people living with COPD, due to long-term steroid use, I have developed osteopenia. This means I can't coach football anymore, as my doctor advised me that kicking a football puts me at great risk of breaking a bone. Another symptom that impacts my life is COPD-related fatigue. I have trouble falling asleep and wake up frequently, as I have a hard time breathing at night.

	COPD can be a very isolating disease, particularly during winter when I am more vulnerable to infections. Common Infections, such as a cold, flu or sinus infection, can trigger increased symptoms and lead to a flare-up or an exacerbation. Due to my breathlessness, I have missed many family events with my grandchildren. I can't go see my Grandson play football, as I struggle to walk to the pitch. I have been a lifelong supporter of Leicester City, and I am a season ticket holder. However, in recent years, when my COPD symptoms have gotten worse, so I struggle to go to matches.
7a. What do you think of the current treatments and care available for moderate to severe COPD on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages for patients of current NHS treatments for moderate to severe COPD (for example, how they are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of dupilumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does dupilumab help to overcome or address any of the listed disadvantages of current treatment that**	Biologic treatments like dupilumab give me hope that I will have a better life quality and not live with worry about my next exacerbation. I have seen first-hand the transformative impact of biologics when I participated in research trials for astegolimab and mepolizumab. When I was on a biologic, my symptoms and quality of life hugely improved. For the first time in years, I didn't have an exacerbation, and my lung function significantly improved. During the trials, I was also able to reduce my steroid dose. For me, this is a huge advantage of biologics, as I suffer from terrible adverse side effects from long-term use of steroids.

you have described in question 8? If so, please describe these	
10. If there are disadvantages of dupilumab over current treatments on the NHS please describe these. For example, are there any risks with dupilumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from dupilumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering COPD and dupilumab? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme	

Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	In the future, I hope that biologics like dupilumab can help patients like me get their life back. I believe that having access to such a treatment would help me gain back my freedom and live a more fulfilling life.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

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BMJ TAG

Dupilumab for treating moderate to severe chronic obstructive pulmonary disease [ID6235]

STA Report

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This report was commissioned by the NIHR Evidence Synthesis Programme as project number 169599.

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Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Clare Dadswell	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background and clinical results sections
Melina Vasileiou	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and assisted with drafting the clinical results sections
Kate Ennis	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Archie Walters	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence.

All authors read and commented on draft versions of the EAG report.

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List of Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
BD	Bronchodilator
BNF	British National Formulary
CI	Confidence interval
CEAC	Cost-effectiveness acceptability curve
CFR	Case fatality rate
CPRD	Clinical Practice Research Datalink
COPD	Chronic Obstructive Pulmonary Disease
CQ	Clarification question
CS	Company submission
CT	Computed tomography
CV	Cardiovascular
EAG	External Assessment Group
EMA	European Medicines Agency
EOS	Eosinophils
EQ-5D-3L	European Quality of Life 5 Dimensions 3 Level Version
E-RS	Evaluating respiratory symptoms in COPD
FeNO	Fractional exhaled nitric oxide
FEF	Forced expiratory flow
FEV_1	Forced expiratory volume in the first second
FVC	Forced vital capacity
GLM	Generalised linear model
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General practitioner
HES	Hospital episode statistics
HPA	Hospital Pharmacy Audit
HR	Hazard ratio
HRQoL	Health-related quality of life
HSE	Health Survey for England
HTA	Health technology appraisal
ICS	Inhaled corticosteroids
ICER	Incremental cost effectiveness ratio
ICS	Inhaled corticosteroid
IRR	Incidence rate ratio
ITC	Indirect treatment comparison
ITT	Intention-to-treat
KM	Kaplan-Meir

LABA	Long-acting beta agonist
LAMA	Long-acting muscarinic antagonist
LS mean	Least squares mean
MAIC	Matching-adjusted indirect comparison
MCID	Minimal clinically important difference
NACAP	National Asthma and Chronic Obstructive Pulmonary Disease Audit Programme
NICE	National Institute of Health and Care Excellence
NG	NICE guideline
NHS	National Health Service
NMA	Network meta-analysis
OWSA	One-way sensitivity analyses
PAS	Patient access scheme
$ppFEV_1$	Percent predicted forced expiratory volume
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
QALY	Quality Adjusted Life Year
QoL	Quality of life
RCT	Randomised controlled trial
SABA	Short-acting beta agonist
SAMA	Short-acting muscarinic antagonist
SGRQ	St George's Respiratory Questionnaire
SLR	Systematic literature review
SMR	Standardised mortality rate
STA	Single Technology Appraisal
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TSD	Technical support document
WTP	Willingness to pay

1 Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1 presents a summary of the EAG's key issues on the evidence submitted on the clinical and cost effectiveness of dupilumab for treating moderate to severe chronic obstructive pulmonary disease (COPD).

Table 1. Summary of key issues

ID	Summary of issue	Report sections
1	Impact of COVID-19 on study design and results	3.2 and 3.3
2	Lack of clinically validated MCIDs	3.3
3	Lack of robust data for roflumilast comparisons	3.4
4	Overestimate of long-term annual decline in FEV_1 through applying an additional multiplier for patients with EOS≥300.	4.2.4.3
5	Uncertainty in difference in the rate of severe exacerbations between treatment arms	4.2.5.3
6	Uncertainty in long-term treatment effect maintenance period of dupilumab.	4.2.5.3
7	Double counting of mortality impact through inclusion of an additional excess mortality case fatality rate (CFR) for severe exacerbations.	4.2.7.1
8	No evidence for the company's use of treatment arm specific utility values	4.2.9.4

Abbreviations: CFR, case fatality rate; EAG, External Assessment Group; EQ-5D-5L, EOS, eosinophils; European Quality of Life 5 Dimensions 5 levels; FEV_1, forced expiratory volume in 1 second; HRQoL, health-related quality of life; ITC, indirect treatment comparison; MCID, minimal clinically important difference; SGRQ, St George's Respiratory Questionnaire

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- Inclusion of excess mortality for severe exacerbations via a case fatality rate (CFR).

- Rate of annual decline in patients forced expiratory volume in one second (FEV_1) over time.
- Use of treatment arm specific utility values.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing the proportion of patients remaining in more moderate COPD health states for longer;
- Reducing the rate of moderate and severe exacerbations.

Overall, the technology is modelled to affect costs by:

- Higher acquisition costs compared to current standard treatment of background therapy alone;
- Higher administration costs;
- Lower COPD severity management costs;
- Lower costs for exacerbation management.

The modelling assumptions that have the greatest effect on the ICER are:

- Modelling of excess mortality for exacerbations;
- Treatment effect maintenance period.

1.3 The clinical and cost effectiveness evidence: summary of the EAG's key issues

Table 2. Issue 1: Impact of COVID-19 on study design and results

Report section	3.2 and 3.3
Description of issue and why the EAG has identified it as important	The key trials for this submission, BOREAS and NOTUS, took place during the COVID-19 pandemic. The CS discusses the impact of the pandemic on both the study design and outcome assessment. The EAG notes that research suggests that people with COPD had fewer exacerbations during the pandemic. It is therefore possible that, with fewer exacerbations in the placebo arm, the effects of dupilumab could be underestimated in the trials. However, if both groups have a similar reduction in exacerbations, then the relative effects of treatment may not be affected. The potential effects of having a COVID-19 infection should also be considered. The company planned to report subgroup data for participants who were impacted by COVID-19 (those who had any major deviation from the trial protocol, or who discontinued the treatment or study due to factors relating to COVID-19) if more than 10% of participants were impacted. However, as this threshold was not reached, subgroup analyses were not conducted. However, the EAG notes that 9.0% of patients in the dupilumab arm and 8.8% of patients in the placebo arm reported TEAEs due to COVID-19 and any impact of this on their response to treatment should be considered.
What alternative approach has the EAG suggested?	The EAG requested subgroup analyses for any participants who reported TEAEs due to COVID-19. This information was provided by the company for annualised rate of moderate or severe COPD exacerbations, pre-bronchodilator FEV_1 and SGRQ score. Differences between dupilumab and placebo were smaller for people who reported a TEAE due to COVID-19 than those who did not. This could indicate that the inclusion of people who had a COVID-19 infection in the analyses resulted in an underestimation of the effects of dupilumab. Despite this, results were similar for the subgroup who did not report a TEAE due to COVID-19 and the overall analysis, indicating that the pandemic may not have had a substantial impact on the results. However, as the precise effects of COVID-19 are unclear, it should be a consideration when discussing the potential effects of dupilumab.
What is the expected effect on the cost-effectiveness estimates?	The EAG considers the impact of COVID-19 on the cost-effectiveness estimates to be unknown, however, if the treatment effect is similar for those who experienced COVID-19 and those who did not, then the impact on the ICER would be minimal.
What additional evidence or analyses might help to resolve this key issue?	There is no specific evidence or analyses that is expected to resolve this issue. The timing of the COVID-19 pandemic in relation to the trials was unavoidable and the company have reported that it had a limited effect on trial design.

Abbreviations: COPD, Chronic obstructive pulmonary disease; CS, company submission; EAG, External Assessment Group; FEV_1, forced expiratory volume in 1 second; SGRQ, Saint George's Respiratory Questionnaire; TEAE, treatment-emergent adverse event.

Table 3. Issue 2: Lack of clinically validated minimal clinically important differences

Report section	3.3
Description of issue and why the EAG has identified it as important	The company provided MCIDs for four outcomes (exacerbation rate, change in FEV_1, SGRQ and E-RS). Only the MCID for change in SGRQ was clinically validated, resulting in uncertainties for the other outcomes when

	considering if the benefits of dupilumab over placebo are clinically meaningful.
What alternative approach has the EAG suggested?	The EAG requested justification for the choice of each threshold, and while this was provided, there was no evidence of validation for the thresholds used for exacerbation rate, change in FEV_1 or E-RS. Consequently, the EAG considered the company's suggested thresholds when interpreting the results but did not use them as the sole decision point when considering if a difference was clinically meaningful. Thresholds considered for each of the three outcomes were: • Exacerbation rate: Company's suggestion that any statistically significant reduction in exacerbations was clinically meaningful and the EAG considered the average magnitude of the reduction in exacerbations per patient; • Change in FEV_1: Company's suggestion of a statistically significant reduction in FEV_1 of 100 ml; • E-RS: A statistically significant reduction in score and the company's suggestion of a 3.7 point reduction.
What is the expected effect on the cost-effectiveness estimates?	The EAG considers the impact of a lack of MCIDs on the cost-effectiveness estimates to be unknown. However, there is a potential risk that the cost-effectiveness results are being driven by statistically significant differences that are not clinically meaningful to the average patient.
What additional evidence or analyses might help to resolve this key issue?	Additional clinically validated MCIDs would help to reduce uncertainties when considering if dupilumab results in clinically meaningful improvements in a patient's COPD symptoms compared to placebo. While most outcomes showed a statistically significant improvement with dupilumab, it is currently unclear whether this represents a meaningful difference in clinical practice.

Abbreviations: COPD, Chronic obstructive pulmonary disease; EAG, External Assessment Group; E-RS, Evaluating Respiratory Symptoms in COPD; FEV_1, forced expiratory volume in 1 second; MCID, minimal clinically important difference; SGRQ, Saint George's Respiratory Questionnaire.

Table 4. Issue 3: Lack of robust data for roflumilast comparisons

Report section	3.4
Description of issue and why the EAG has identified it as important	No evidence directly compared dupilumab to roflumilast, leading the company to use Bucher ITCs to compare the two treatments. However, the CS reports key differences between the dupilumab and roflumilast trials, including differences in background treatments and COPD severity. There are also concerns about the breaking of randomisation in the *post-hoc* analysis used as the source of evidence for roflumilast. These concerns lead to considerable uncertainty when interpreting the results of the ITCs. There is therefore a lack of robust data against which to compare the effectiveness of dupilumab and roflumilast.
What alternative approach has the EAG suggested?	The EAG notes that the use of a MAIC could have addressed some of the differences in populations with fewer methodological concerns than the Bucher ITCs. However, it would be subject to similar concerns about background treatments and COPD severity, leading to similar uncertainties when interpreting the results.
What is the expected effect on the cost-effectiveness estimates?	The company's model includes an option to include roflumilast as a comparator. In a full incremental analysis, background therapy alone is dominated due to higher costs and lower QALYs than roflumilast. The

	resulting ICER for dupilumab plus background therapy compared to roflumilast is £38,398 (deterministic). However, the EAG considers this to be highly uncertain due to the discussed reasons.
What additional evidence or analyses might help to resolve this key issue?	Without either direct evidence, or indirect evidence in a population more closely matched to the dupilumab trials, it is difficult to resolve this issue. However, both the company's and the EAG's clinical experts highlighted that roflumilast is not commonly used in clinical practice, and while it could be an additional treatment, it is not expected to be an alternative option for patients who will be eligible for dupilumab. As such, the lack of robust data for roflumilast may be less of a concern than if it was an alternative treatment option that was commonly used in practice.

Abbreviations: COPD, Chronic obstructive pulmonary disease; CS, company submission; EAG, External Assessment Group; ITC, indirect treatment comparison; MAIC, matched-adjusted indirect comparison.

Table 5. Issue 4: Overestimate of long-term annual decline in FEV_1

Report section	Section 4.2.4.3
Description of issue and why the EAG has identified it as important	To estimate transition probabilities between COPD severity health states, the company utilised estimates of long-term decline in FEV_1 from Fenwick *et al.,* which provided estimates separately for patients with no recent exacerbation or recent exacerbation. As this study was not specifically based on patients with EOS≥300, the company applied a multiplier to the Fenwick *et al.* FEV_1 decline in order to represent increased rates of annual decline for patients with EOS≥300. The EAG notes that the estimates from Fenwick *et al.* were based on patients receiving dual background therapy, which may have resulted in an overestimate of the rate of decline compared to patients receiving triple background therapy, such as the population in the current appraisal. The EAG considers that applying an additional multiplier may therefore further overestimate the annual rate of decline, particularly due to additional concerns the EAG has with the data used to inform the multiplier.
What alternative approach has the EAG suggested?	The EAG considers it more appropriate to inform transitions between COPD severity health states based on the annual decline estimated by Fenwick *et al.*, without an additional adjustment of a multiplier for EOS≥300.
What is the expected effect on the cost-effectiveness estimates?	The company base case post clarification probabilistic ICER increased from £23,518 to £24,481.
What additional evidence or analyses might help to resolve this key issue?	The EAG is not aware of any available data that would address this uncertainty.

Abbreviations: COPD, chronic obstructive pulmonary disease; EAG, External Assessment Group; EOS, eosinophil count; FEV_1, forced expiratory volume in one second; ICER, incremental cost-effectiveness ratio

Table 6. Issue 5: Uncertainty in differences in the rate of severe exacerbations between treatment arms

Report section	Section 3.3.2.2 and 4.2.5.3
Description of issue and why the EAG has identified it as important	The pooled data from BOREAS and NOTUS showed a statistically significant decrease in the combined rate of moderate and severe exacerbations for patients treated with dupilumab. However, there was no statistically significant difference in severe exacerbations between the two treatment arms in the 52-week trial period and 90% of exacerbations experienced were moderate.

	Although the EAG is aware that the trial was not powered to detect statistically significant differences in severe and moderate exacerbations separately, it is noted that differences in severe exacerbations are a key driver of the ICER, due to the associated impact on costs, quality of life and mortality. As a difference in exacerbations is modelled for a patient's lifetime while they remain on dupilumab, the EAG considers the benefit may be overestimated.
What alternative approach has the EAG suggested?	Due to the uncertainty in the magnitude of the reduction in severe exacerbations, the EAG included two illustrative scenario analyses in which the difference in severe exacerbations between the two treatment arms is removed and an additional example in which the treatment benefit on severe exacerbations is halved
What is the expected effect on the cost-effectiveness estimates?	Removing the treatment effect on severe exacerbations had a large increase in the ICER, increasing the company's post clarification base case probabilistic ICER to £55,427. The additional example in which the treatment benefit was halved resulted in an increase to the company's base case ICER to £36,629. The EAG notes that this scenario was only implemented in the model deterministically.
What additional evidence or analyses might help to resolve this key issue?	Based on the trial data available, the EAG consider that there is no available evidence or analyses that is expected to resolve this issue.
Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio	

Table 7. Issue 6: Uncertainty in long-term treatment effect maintenance period of dupilumab.

Report section	Section 4.2.5.3
Description of issue and why the EAG has identified it as important	The company's base case assumes a treatment effect maintenance period for dupilumab of three years, during which patients annual FEV_1 does not decline. This is based on data from dupilumab in patients with moderate or severe asthma, in light of lack of long-term data in COPD patients receiving dupilumab beyond the 52-week trial period. While clinical experts to the EAG noted that this may be a reasonable assumption, it was highlighted that COPD patients are likely to be older with more comorbidities than asthma patients which could result in them experiencing lung function decline sooner than the asthma population.
What alternative approach has the EAG suggested?	While the EAG used the same assumption as the company in the EAG base-case analysis, based on a lack of long-term data in the population of interest, the treatment effect maintenance period is considered to be highly uncertain in the economic model. Therefore, the EAG included alternative scenarios using a shorter treatment effect maintenance period (two years and one year).
What is the expected effect on the cost-effectiveness estimates?	Using a two-year treatment effect period increased the company's post clarification base case probabilistic ICER from £23,518 to £25,391, while using a one-year treatment effect period increased the ICER to £28,914. The EAG notes that due to the smaller incremental QALYs in the EAG base-case analysis (see Section 6.4), the treatment effect maintenance period has a much greater impact on the resulting EAG base-case ICER, with a treatment effect period of one year (i.e.no effect beyond the trial period) resulting in an ICER of £137,497.

What additional evidence or analyses might help to resolve this key issue?	The EAG considers that the uncertainty around the long-term effectiveness on patients FEV_1 assumed in the model can only be overcome by additional data collection on COPD patients receiving dupilumab, beyond the 52-week trial period. As patients had dupilumab withdrawn at the end of NOTUS and BOREAS, the EAG notes that these data are not expected to be available. In light of a lack of available data, the EAG notes that the company and EAG base-case assumptions and corresponding ICERs should be considered as optimistic.

Abbreviations: COPD, chronic obstructive pulmonary disease; EAG, External Assessment Group; EOS, eosinophil count; FEV1, forced expiratory volume in one second; ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years.

Table 8. Issue 7: Inclusion of excess mortality for severe exacerbations double counting impact

Report section	Section 4.2.7.1
Description of issue and why the EAG has identified it as important	The company's base-case analysis applies excess mortality associated with each COPD severity stage (measured using airflow limitation GOLD stages 1–4), sourced from Whittaker *et al*. 2024.[1] This study estimated all-cause mortality hazard ratios (HRs) associated with COPD severity based on a UK dataset. In addition, a separate case fatality rate (CFR) is applied in the model for severe exacerbations. Whittaker *et al*. 2024 controlled for recent exacerbation history in the regression models used to estimate the hazard ratio associated with COPD severity. Therefore, the EAG considers that applying a separate CFR will double count the impact of exacerbations on mortality that may already have been accounted for within the COPD severity mortality. In addition to double counting, the EAG considers the source used for the CFR to also be inappropriate due to being based on a meta-analysis of six non-UK based studies which are considered to relatively out of date (and so not reflective of current UK clinical practice). The EAG notes that the modelling of excess mortality is the main driver of the ICER and therefore the EAG consider this to be the key issue of the appraisal.
What alternative approach has the EAG suggested?	A range of alternative scenarios have been applied by both the company and the EAG. Due to the risk of double counting, the EAG prefers the removal of the CFR for severe exacerbations in the EAG base-case analysis. Alternative scenarios have also been included as EAG scenario analyses, including the use of alternative sources for the excess mortality related to exacerbations, which the EAG considers to be potentially more appropriate. During clarification, the company included a number of alternative scenarios for modelling mortality, including removing the CFR but applying separate treatment arm specific HRs. This was applied by adjusting the HRs from Whittaker *et al.* 2024 in the dupilumab arm which the company considered the best alternative to their base-case analysis. When implemented correctly

	by the EAG, this resulted in an ICER of £35,607 (deterministic as the EAG was unable to implement the change probabilistically). The EAG also notes that there is no evidence of a mortality benefit of dupilumab from the available data from NOTUS and BOREAS.
What is the expected effect on the cost-effectiveness estimates?	Removal of the CFR for severe exacerbations had a substantial impact on the ICER, increasing the company's post clarification base case probabilistic ICER to £51,884. Some of the company's included scenario analyses using alternative sources for the COPD severity mortality and retaining the CFR for severe exacerbations resulted in small changes in the company's base-case ICER. However, the EAG notes that the same issues of double counting and inappropriate data source used for the CFR remain in these scenarios. The EAG's additional scenario which includes excess mortality related to exacerbations sourced from Whittaker *et al*. 2022[2] increases the company's ICER to £33,331. The EAG notes that due to combination with other model assumptions, namely differences in utility values and resulting incremental QALYs, the mortality modelling assumptions used in the EAG's base-case analysis have a greater impact on the ICER than in the company's analysis.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers the range of scenarios provided highlights the sensitivity of the results to the approach taken to modelling excess mortality from severe exacerbations.

Abbreviations: CFR, case fatality rate; COPD, chronic obstructive pulmonary disease; EAG, External Assessment Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years.

Table 9. Issue 8: No evidence for the company's use of treatment arm specific utility values

Report section	Section 4.2.9.4
Description of issue and why the EAG has identified it as important	Health-related quality of life data (HRQoL) in NOTUS and BOREAS was collected using both the St. George's Respiratory Questionnaire (SGRQ) and EQ-5D-5L. However, due to the low collection timepoints of the EQ-5D-5L in NOTUS and BOREAS, the company produced a mapping algorithm which utilised data from visits where both the SGRQ (from the pooled trials) and EQ-5D-5L were collected in order to obtain EQ-5D health state utility values (cross-walked to EQ-5D-3L). The company's base case analysis used treatment arm specific utility values for each COPD severity health state. The regression analysis for utilities showed that only SGRQ at baseline, severity of airflow obstruction, and exacerbation risk were statistically significant. The coefficient for treatment group and the interaction terms between treatment and severity of airflow obstruction groups were not statistically significant (p-values ranging from 0.22 to 0.79). Therefore, the EAG does not consider there to be robust evidence of a separate treatment related benefit to justify using treatment arm specific utilities.

	While the EAG considers the use of HRQoL data collected from the same source as the effectiveness data to be most appropriate, the EAG also has some concerns with the reliability of the mapping analysis and the correlation between the two outcome measures.
What alternative approach has the EAG suggested?	During clarification, the EAG requested a scenario in which the utility regression model was rerun to include only statistically significant covariates (i.e. removal of the treatment interaction term and treatment arm covariates). The resulting health state utility values and exacerbation disutilities are considered more appropriate than the company's use of treatment arm specific utility values.
What is the expected effect on the cost-effectiveness estimates?	The use of utility values derived from the mapping analysis including statistically significant variables increased the company's base case post clarification probabilistic ICER from £23,518 to £25,179. The EAG also included a scenario analysis using utility values preferred by the committee in the previous NICE appraisal of roflumilast (TA461).
What additional evidence or analyses might help to resolve this key issue?	The EAG consider the range of scenarios provided highlight the different options available using alternative sources of evidence.
Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio	

1.4 Other key issues: summary of the EAG's view

A number of additional issues were identified. These have a less significant impact on results than the key issues identified in Section 1.3 but they still represent areas of uncertainty or required the EAG to make changes to the economic model.

1. The NOTUS trial used interim analysis methods, which allowed a database lock when 92% of the information fraction for the primary endpoint was reached, meaning that 21.3% of patients in the trial did not reach the 52-week endpoint. Interim analysis methods can result in an overestimation of treatment effects, and although the EAG considers it is unlikely to have had a major impact on the pooled analysis, it should still be considered when interpreting the results – Section 3.2 and 3.3;
2. The company used data on the baseline rate of exacerbations from the year prior to randomisation in the base-case analysis to account for any underestimation of the exacerbation rate experienced in clinical practice. The EAG notes that FEV_1 would also be expected to be higher during a trial period than a real-world setting, seen through the improvements observed in patients FEV_1 during the trial period in both treatment arms. The EAG prefers the use of a starting distribution of patients in each GOLD stage that removes any 'trial effects' on FEV_1 – Section 4.2.3.3;

3. No further adjustment of the reference exacerbation rate from Whittaker *et al.* 2022 included,[2] used to estimate the future number of exacerbations, for patients who had no exacerbations in the previous year – Section 4.2.4.3;
4. No difference in event rates in non-fatal CV events between treatment arms – Section 4.2.8;
5. Cardiovascular event disutilities informed by Ara and Brazier 2010[3] – Section 4.2.10.3;
6. 5% of patients receive assistance with dupilumab administration, provided by a nurse home visit – Section 4.2.10.4;
7. 37% of severe exacerbation patients followed up after 90 days (i.e. removal of the 18% of patients followed up after 30 days in resource use) – Section 4.2.10.4.

1.5 Summary of EAG's preferred assumptions and resulting ICER

Table 10 presents the EAG's preferred model assumptions and resulting cumulative change in the ICER from the company's base-case analysis. Results of each scenario presented are probabilistic, with the EAG's base-case ICER presented as both deterministic and probabilistic. For further details of the exploratory and sensitivity analyses done by the EAG, see Sections 6.3 and 6.5.

Table 10. EAG preferred assumptions and probabilistic base-case ICER

Preferred assumption	Section in EAG report	Cumulative incremental costs	Cumulative incremental QALYs	Cumulative ICER (£/QALY)
Company base case post clarification	Section 5.1	[redacted]	[redacted]	£23,624
Removal of FEV_1 trial effects	Section 4.2.5	[redacted]	[redacted]	£23,597
COPD severity transition probabilities based on Fenwick *et al.* with no further multiplier applied	Section 4.2.4.3	[redacted]	[redacted]	£24,896
No difference in event rates in non-fatal CV events between treatment arms	Section 4.2.8	[redacted]	[redacted]	£24,816
Utility value informed by mapping of SGRQ from pooled BOREAS and NOTUS trials to EQ-5D-3L, analysis excluding non-significant covariates.	Section 4.2.9.4	[redacted]	[redacted]	£26,504
CV event disutilities informed by Ara and Brazier. 2010	Section 4.2.9.4	[redacted]	[redacted]	£26,129
Dupilumab administration support via home nurse visit (5%)	Section 4.2.10.4	[redacted]	[redacted]	£26,353
37% of severe exacerbation patients followed up after 90 days only	Section 4.2.10.4	[redacted]	[redacted]	£26,382

No excess mortality due to severe exacerbations	Section 4.2.7.1	[redacted]	[redacted]	£73,154
EAG preferred base case (probabilistic)	**-**	[redacted]	[redacted]	**£73,154**
EAG preferred base case (deterministic)	**-**	[redacted]	[redacted]	**£68,832**

Abbreviations: COPD, chronic obstructive pulmonary disease; CV, cardiovascular; EAG, External Assessment Group; EQ-5D-3L, European Quality of Life 5 Dimensions 3 Level Version; FEV_1, forced expiratory volume in one second; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

2 Introduction and background

2.1 Introduction

This report contains the External Assessment Group (EAG)'s critique of the clinical and cost-effectiveness evidence submitted for the Single Technology Appraisal (STA) of dupilumab (Dupixent®, Sanofi) for the treatment of people with moderate to severe chronic obstructive pulmonary disease (COPD). The marketing authorisation for dupilumab in this indication is, "in adults as add-on maintenance treatment for uncontrolled COPD characterised by raised blood eosinophils (EOS) 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". [4] Dupilumab is already recommended as add-on maintenance therapy for the treatment of severe asthma with type 2 inflammation.[5]

2.2 Background

The company submission (CS) provides an overview of COPD, including the causes, prevalence, diagnosis, pathology, and symptom burden (Section B.1.3.1). It also provides a description of dupilumab, its mechanism of action, indication, and methods of administration and dosage (Section B.1.2 of the CS). Included below is the EAG's summary of the key background information presented in the CS, supplemented by information provided by the EAG's clinical experts.

COPD is a progressive respiratory disease which results in irreversible damage to the lungs as a result of chronic inflammation and repeated exacerbations. It is commonly caused by smoking, but can also occur following long-term exposure to other toxic particles or gasses.[6] COPD is one of the top five causes of death in England, and its prevalence is expected to rise further with an ageing population.

Common symptoms associated with COPD include dyspnoea, chronic cough, sputum production, wheezing, chest tightness, exercise intolerance and exacerbations. COPD has a high mortality rate and so it is crucial for symptoms to be controlled and progression of the disease to be slowed. However, current management options for people with moderate to severe COPD are limited, and symptom management can be complex due to the range of comorbidities associated with the disease. Exacerbations, which are a periodic worsening of respiratory symptoms, are common for people with moderate to severe COPD, and often require treatment with either rescue packs (a short course of steroids and antibiotics) or hospital treatment depending on the severity of the exacerbation. People who experience exacerbations more frequently tend to experience a higher

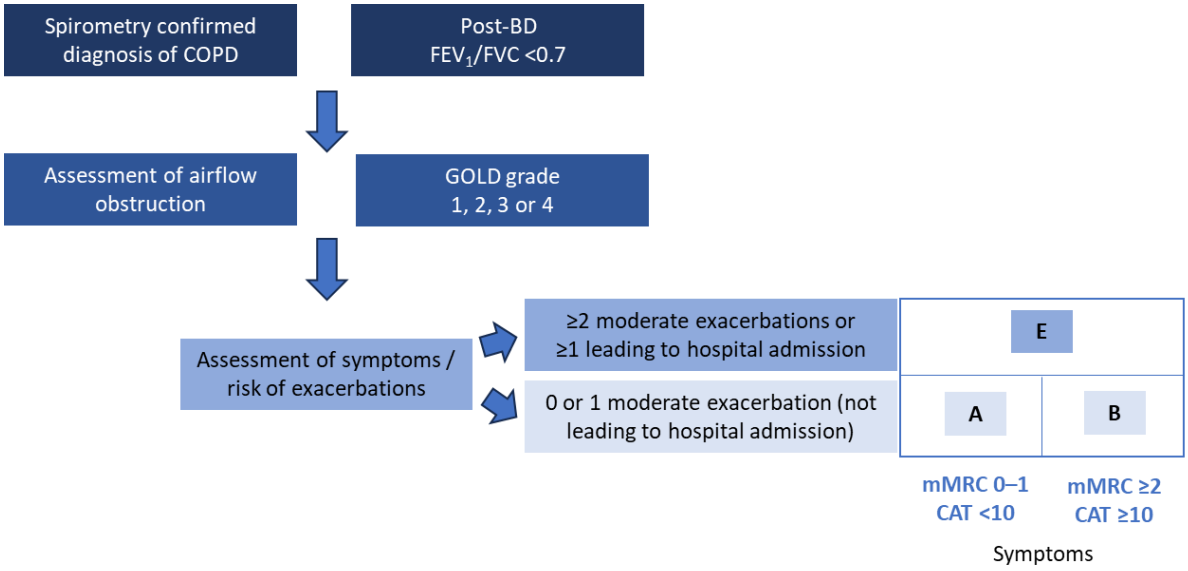
number of cardiovascular events, faster lung function decline and have a higher symptom burden than those who have less frequent exacerbations. Having an exacerbation also puts patients at greater risk of experiencing future exacerbations, making it important to try and reduce the risk of these events occurring.

The focus of the CS is people who have uncontrolled COPD and type-2 inflammation, characterised by raised blood eosinophils (EOS) (≥300 cells/µL). This is one of the key factors in the progression of COPD, with patients who show signs of type-2 inflammation often having a worse prognosis than those who do not have type-2 inflammation. While many of these patients will show improvements with ICS, some will continue to experience exacerbations. For those patients where ICS does not prevent or reduce exacerbations, there are currently no additional treatment options.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2025 Global Strategy for the Diagnosis, Management and Prevention of COPD and the NICE 2019 guidelines for the diagnosis and management of COPD in people ≥16 years of age outline the common symptoms associated with COPD. These include progressive, persistent dyspnoea that is worse with exercise, recurrent wheeze, chronic cough that may be intermittent or that may be productive, and recurrent lower respiratory tract infections (bronchitis). COPD diagnosis is confirmed with the use of spirometry to indicate persistent airflow obstruction. The GOLD and NICE guidelines recommend that diagnosis is made based on post-bronchodilator testing, with a ratio of forced expiratory volume in the first second (FEV_1) to forced vital capacity (FVC) <0.7 indicating an airflow obstruction. Airflow obstruction is categorised as mild, moderate, severe or very severe depending on the post-bronchodilator FEV_1 compared to predicted values.

While post-bronchodilator FEV_1 is an effective method of categorising the severity of airflow obstruction, it cannot accurately predict someone's risk of future exacerbations. Treatment decisions are therefore based on a combination of disease severity and exacerbation history, with guidance provided by the GOLD ABE assessment tool. The GOLD tool categorises patients into one of three groups (A, B or E), with group E representing the patients with the most severe disease and the worst prognosis (Figure 1).Figure 1. Summary of the GOLD ABE assessment tool. Recreated from Figure 1 of the CS, Document B. The CS proposes that a subgroup of the patients in group E should be eligible for dupilumab. Further information about the intended patient population and proposed positioning of dupilumab in the treatment pathway is provided in Section 2.2.1.

Figure 1. Summary of the GOLD ABE assessment tool. Recreated from Figure 1 of the CS, Document B.



Abbreviations: BD, bronchodilator; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council.

2.2.1 *Current treatment pathway*

Although the damage caused by COPD is irreversible, the disease can be controlled, and the progression of symptoms can be slowed. The treatment pathway is outlined in Section B.1.3.2 of the CS, with the company noting two treatment pathways, the first recommended by NICE,[7] and the second provided by the GOLD Global Strategy.[6] NICE recommends that initial treatment should involve optimising the fundamentals of care, which includes support to stop smoking, providing pneumococcal and influenza vaccinations, pulmonary rehabilitation if needed, creating individual self-management plans and optimising treatment for comorbidities. Once the fundamentals of care are provided, patients should be offered either a short-acting β2 agonist (SABA) or short-acting muscarinic antagonist (SAMA). If a patient continues to experience symptoms following initial treatment, they can instead be prescribed double therapy (either a long-acting β2 agonist and long-acting β2 agonist [LABA + LAMA] or LABA and inhaled corticosteroids [LABA + ICS]). If symptoms persist despite double therapy, and a patient can tolerate ICS treatment, they can then be prescribed triple therapy (LABA, LAMA and ICS). The GOLD Strategy recommends either a SABA or LABA for people in group A of the ABE assessment (Figure 1), or LABA + LAMA for those in group B. Triple therapy is considered for those in group E who continue to experience exacerbations and have blood EOS ≥300 cells/µl. Some of the EAG's clinical experts noted that the use of a SABA or SAMA as

initial treatment is now becoming less common, reflecting the recommendations in the GOLD Strategy. However, the EAG does not anticipate that the differences in initial treatment between the NICE guidelines and the GOLD Strategy are likely to impact on the assessment of dupilumab, as patients who are proposed to be eligible for dupilumab will be at a later stage in the treatment pathway.

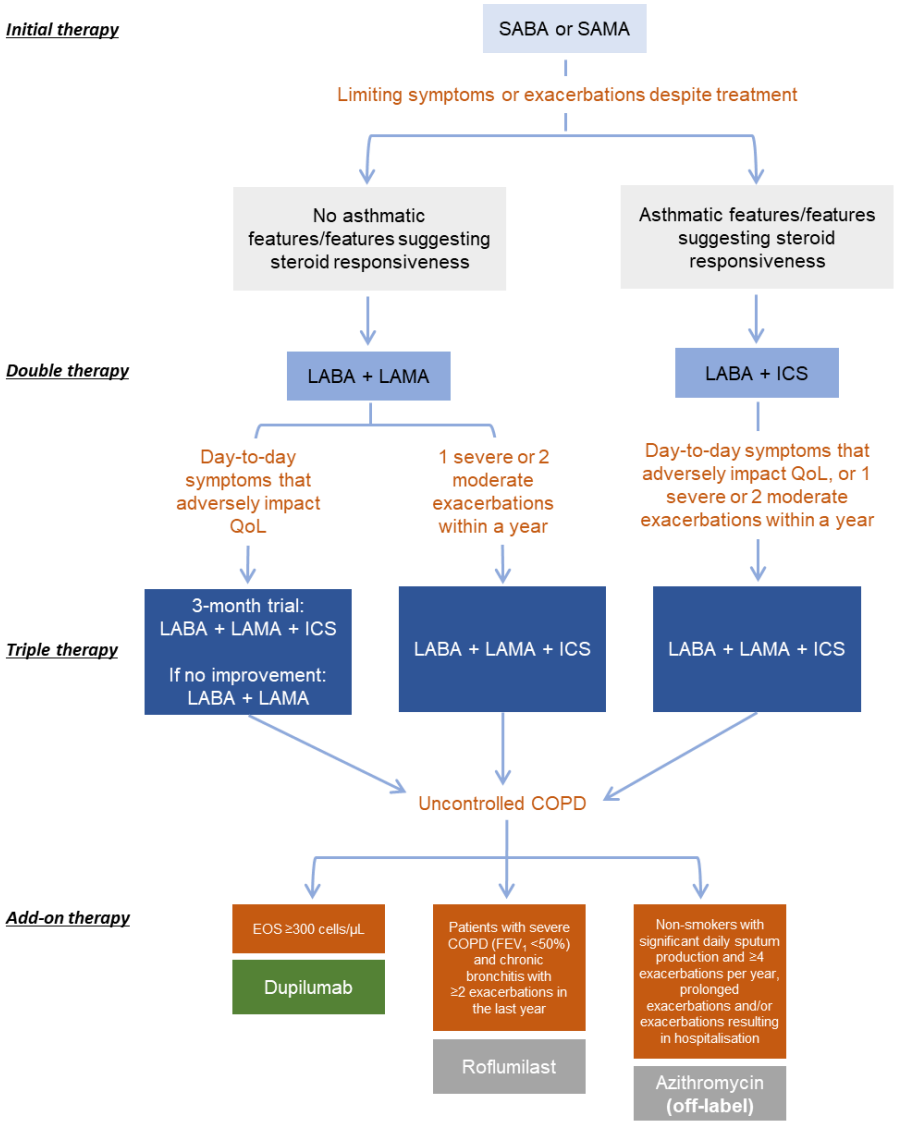
The final stage in the treatment pathway for patients who continue to experience exacerbations following triple therapy is the option of add-on therapy. In current practice, add-on therapy consists of two options:

1. Roflumilast for patients with severe COPD (FEV_1<50%) and chronic bronchitis with ≥2 exacerbations in the previous year; or
2. Azithromycin as an off-label option for non-smokers with significant daily sputum production and ≥4 exacerbations per year, prolonged exacerbations, or exacerbations resulting in hospitalisation.

While both roflumilast and azithromycin can both have benefits, they also have contraindications and are associated with a number of side-effects, discussed in more detail in Sections 2.3.3.2 and 2.3.3.3. The CS notes that roflumilast is not commonly used in practice for patients with COPD, and both roflumilast and azithromycin have limited overlap with the patient population that is proposed for dupilumab (see Sections 2.3.3.2 and 2.3.3.3).

Dupilumab is proposed as an add-on treatment for a subgroup of the patients who have exacerbations despite triple therapy. The marketing authorisation is for patients in this group who also have raised blood EOS (defined by the company as ≥300 cells/µL), as this indicates Type 2 inflammation which puts people at greater risk of moderate or severe exacerbations. The company's suggested positioning of dupilumab, following provision of the fundamentals of care, is outlined in Figure 2. As discussed above, some of the EAG's clinical experts noted that SABA and SAMA are now used less frequently in practice, and LABA + ICS are not commonly used. However, the position of dupilumab relative to triple therapy and the other options for add-on therapy matches the positioning expected by the EAG's clinical experts.

Figure 2. Current COPD treatment pathway based on NICE 2019 guidelines, including the proposed positioning of dupilumab. Recreated from Figure 11 of the CS, Document B.



Abbreviations: COPD, chronic obstructive pulmonary disease; EOS, eosinophils; FEV_1, forced expiratory volume in the first second; ICS, inhaled corticosteroids; LABA, long acting beta agonist; LAMA, long acting muscarinic antagonist; QoL, quality of life; SABA, short-acting beta agonist; SAMA, short acting muscarinic antagonist

2.3 Critique of the company's definition of the decision problem

The company provided a summary of the final scope issued by the National Institute for Health and Care Excellence (NICE), together with a rationale for any deviations from the decision problem. The CS covers the full marketing authorisation for dupilumab and matches the majority of the NICE final scope, with an update to the description of the population, and some differences in the comparators. Overall, the EAG considers that the CS appears appropriate and justified. A summary of the final scope issued by NICE, the decision problem addressed in the CS, and the EAG's critique of

this is provided in Table 11. Further detail about the EAG's critique is provided in Sections 2.3.1 to 2.3.3.3.

Table 11. Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
Population	Adults with moderate to severe COPD and raised EOS who have uncontrolled disease on triple inhaled therapy or double therapy where ICS is not appropriate	Adults with uncontrolled COPD (≥2 moderate or ≥1 severe historical exacerbations within 12 months) with raised blood eosinophils (EOS ≥300 cells/μL), on triple therapy (LABA + LAMA + ICS) or double therapy (LABA + LAMA) if ICS is not appropriate.	The scope wording anticipated the label, which became available after the final scope was issued. The label does not include the term 'moderate to severe' or provide definitions for 'uncontrolled' or 'raised EOS'. The company have aligned the definition of 'uncontrolled' to the GOLD group E criteria and pivotal trial inclusion criteria for prior exacerbations. (≥2 moderate or ≥1 severe historical exacerbations within 12 months). The company defined 'raised EOS' as ≥300 blood eosinophils/μL. The company stated that these changes reflect the full licence for dupilumab.	The population in the submission states that people should have uncontrolled COPD, rather than the definition of moderate to severe COPD which was stated in the NICE final scope. The company's definition matches the marketing authorisation for dupilumab, and so this appears appropriate. The definition used for uncontrolled COPD (≥2 moderate or ≥1 severe historical exacerbations within 12 months) aligns with the population in group E of the GOLD guidelines and was considered reflective of clinical practice by the EAG's clinical experts. No threshold for raised EOS was provided in the final NICE scope, but the submission specifies this as ≥300 cells/μL. The company stated that this is in line with the key trial inclusion criteria and the EAG's clinical experts agreed that this is an appropriate threshold. The EAG therefore considers this a reasonable addition to the definition in the NICE final scope.

Intervention	Dupilumab as an add-on to triple inhaled therapy or double therapy where ICS is not appropriate.	Per NICE scope	N/A	N/A
Comparator(s)	• Standard care without dupilumab (triple inhaled therapy or double therapy where ICS is not appropriate) • Roflumilast in combination with a long-acting muscarinic antagonist, a long-acting beta-2 agonist and an inhaled corticosteroid (for people who had 2 or more exacerbations in the previous 12 months despite triple inhaled therapy) • Azithromycin	• Standard care without dupilumab (triple inhaled therapy or double therapy where ICS is not appropriate) • Roflumilast in combination with a long-acting muscarinic antagonist, a long-acting beta-2 agonist and an inhaled corticosteroid (for people who had 2 or more exacerbations in the previous 12 months despite triple inhaled therapy) Azithromycin is not considered as a comparator.	The company does not consider azithromycin a relevant comparator because it: • Lacks clinical evidence supporting use in the dupilumab-eligible population. • Is not approved for the treatment of COPD in England. Although off-label use is recommended by NICE, its use is limited to non-smokers who continue to have ≥4 exacerbations per year, which differs from the dupilumab-eligible population. • Has a high risk of severe AEs, including CV events, imposes additional testing and ongoing monitoring and has a high potential for the development of antibiotic resistance, limiting its use in clinical practice. • Is being reviewed by the EMA with the aim of restricting its use due to	The company stated that azithromycin is not a relevant comparator because it can only be used off-label for COPD and is associated with a risk of severe adverse events and an increase in antibiotic resistance. The EAG's clinical experts noted that, while azithromycin might be considered in addition to dupilumab in clinical practice, it would not be an alternative treatment option for people with raised EOS. The EAG therefore considers that the different indications for the two treatments makes the company's assertion that azithromycin is not a relevant comparator reasonable.

			concerns over antibiotic resistance.	
Outcomes	• Lung function • Incidence and severity of acute exacerbations • Symptom control • Mortality • AEs of treatment • HRQoL	• Lung function (Change in pre-BD FEV_1) • Incidence and severity of acute exacerbations (Adjusted annualised rate of moderate or severe exacerbations) • Symptom control (Change in E-RS) • Mortality • AEs of treatment • HRQoL (Change in SGRQ)	N/A	N/A
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent	As per the final scope, with the exception that Azithromycin is not considered as a comparator in the economic model, as per the above mentioned reasons. Roflumilast is included in the economic model as a scenario analysis only.	N/A	The economic analysis adheres to the reference case

	treatment technologies will be taken into account			
Subgroups to be considered	• High EOS (≥500 cells/μL) • High FeNO (≥20 ppb)	Per NICE scope	N/A	N/A
Special considerations, including issues related to equity or equality	N/A	N/A	N/A	N/A

Abbreviations: AEs, adverse events; BD, bronchodilator; COPD, Chronic Obstructive Pulmonary Disease; CV events, cardiovascular events; EAG, External Assessment Group; EMA, European Medicines Agency; EOS, eosinophils; E-RS, Evaluating respiratory symptoms in COPD; FeNO, Fractional exhaled nitric oxide; FEV_1, Forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HRQoL Health-related quality of life; ICS, Inhaled corticosteroid; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic agonist; μL, microlitres; NHS, national health service; NICE, National Institute for Health and Care Excellence; ppb, parts per billion; PSS, Personal Social Services; QALY, Quality Adjusted Life Year; SGRQ, St George's Respiratory Questionnaire.

2.3.1 Population

Alignment to NICE final scope and population in England

The NICE final scope focuses on all adults with moderate to severe COPD and raised EOS who have uncontrolled disease on triple inhaled therapy or double therapy where ICS is not appropriate. The final scope was published before the final marketing authorisation for dupilumab in COPD was available, resulting in differences in the terminology used in the two documents. The company therefore modified the wording of the population once the marketing authorisation was available, focusing on people who have uncontrolled COPD with raised blood EOS, on triple inhaled therapy or double therapy where ICS is not appropriate. Given that the company's definition matches the marketing authorisation for dupilumab in COPD, these changes appear appropriate.

The company defined uncontrolled COPD as ≥2 moderate or ≥1 severe historical exacerbations within 12 months, which aligns with the population in group E of the GOLD guidelines. The EAG's clinical experts considered this definition to be reasonable and reflective of clinical practice. The threshold provided for raised blood EOS was ≥300 cells/μL, which matches the inclusion criteria for the key trials in this appraisal. The EAG's clinical experts noted that this threshold is often used as an indicator that ICS would be an effective treatment for patients with COPD, as well as being used in asthma when identifying patients who are likely to respond to biologic treatment. As such, this appears to be an appropriate threshold to use as a marker for raised blood EOS.

Inclusion criteria for the key trials in this appraisal (BOREAS and NOTUS) were discussed with the EAG's clinical experts. Both used the same inclusion criteria:

- Aged ≥40 to ≤80 years;
- Physician diagnosis of COPD;
- Current or former smokers with a smoking history of ≥10 pack-years;
- Moderate-to-severe COPD;
- MRC dyspnoea score of grade ≥2a;
- Patient-reported history of signs and symptoms of chronic bronchitis for 3 months in the year up to screening in the absence of other known causes of chronic cough;
- History of ≥2 moderate or ≥1 severe exacerbations in the year prior to inclusion;
- ≥1 exacerbation occurring while on treatment with LABA + LAMA + ICS (or LABA + LAMA, if ICS was not appropriate;

- One moderate exacerbation requiring the use of systemic corticosteroids;
- Background triple therapy (or double therapy if ICS not appropriate) for three months prior to randomisation with a stable dose of medication for ≥1 month prior to Visit 1; and
- Blood EOS ≥300 cells/µL at screening.

The EAG's clinical experts considered these criteria to be an accurate reflection of the patients they see in clinical practice. They thought it was reasonable to only include people who were current or former smokers with a smoking history of ≥10 pack-years, given that most cases of COPD in the UK are smoking-related. The EAG noted that the inclusion criteria of the NOTUS trial were modified from people aged between 40 and 80 years to those aged between 40 and 85 years. However, while older people may have more comorbidities, the EAG's clinical experts did not expect this change to introduce any major differences in treatment effectiveness or safety.

One potential limitation of the BOREAS and NOTUS trials was the small number of patients from England. The NOTUS trial included 12 patients from 11 sites in England, and no English sites were included in BOREAS. This could limit the generalisability of the results if patient characteristics or clinical practice differ considerably between the countries included in the trial and those in the NHS. However, the CS states that clinical experts considered the populations in both trials to be generalisable to the patient population that would be eligible for dupilumab in England. This view was supported by the EAG's clinical experts who noted that the baseline characteristics reflected what they would expect to see in clinical practice. As such, the location of the trials does not appear to be a major concern. All other inclusion criteria and baseline characteristics appeared reasonable and so the EAG considers that the submission reflects the patient population in the decision problem.

2.3.2 Intervention

The intervention matches that stated in the NICE final scope. Dupilumab (brand name Dupixent®) has a marketing authorisation for adults as add-on maintenance treatment for uncontrolled COPD characterised by raised blood EOS on a combination of an ICS, a LABA, and a LAMA (triple therapy), or on a combination of a LABA and a LAMA (double therapy) if ICS is not appropriate.

Dupilumab is a recombinant human IgG4 monoclonal antibody that inhibits IL-4 and IL-13 signalling, both of which are associated with Type 2 inflammatory disease, including COPD. By inhibiting the

action of IL-4 and IL-3, dupilumab decreases the mediators of Type 2 inflammation, which can otherwise result in more serious outcomes for patients with COPD. The recommended dose for dupilumab is 300 mg every other week, administered using a subcutaneous injection via either a pre-filled syringe or pen. Most people can self-administer dupilumab at home, although some may need a carer or healthcare worker to administer the injection for them. The EAG's clinical experts noted that the number of people who would need assistance in delivering dupilumab would be relatively small.

The BOREAS and NOTUS trials assessed the use of dupilumab over 52 weeks, and the EAG's clinical experts considered this to be an acceptable time over which to assess someone's response to treatment. They noted that patients would likely remain on treatment beyond 52 weeks if they did show a response. Given that the dose, method of administration and assessment time points reflect what the clinical experts would expect in practice, the intervention used in the trials appears suitable to address the decision problem.

2.3.3 Comparators

2.3.3.1 Standard care without dupilumab

The CS presents standard care as the primary comparator, in line with the NICE final scope and reflecting the current NHS treatment pathway for most patients who would be eligible for dupilumab. As discussed in Section 2.2.1, people who continue to experience COPD exacerbations despite initial treatment are prescribed triple inhaled therapy, or double therapy if ICS is not appropriate. In clinical practice, there are currently no additional long-term treatments available if a person continues to experience symptoms despite inhaled therapies, unless they are eligible for either roflumilast or azithromycin (outlined in Sections 2.3.3.2 and 2.3.3.3). Instead, exacerbations are treated using steroids and/or antibiotics with bronchodilators, with hospital treatment often required for the most severe exacerbations. The EAG's clinical experts confirmed that the standard of care presented in the BOREAS and NOTUS trials reflects clinical practice in England, and the results are therefore considered generalisable to the NHS.

2.3.3.2 Roflumilast in combination with a long-acting muscarinic antagonist, a long-acting beta-2 agonist and an inhaled corticosteroid

Roflumilast is indicated as an add-on to bronchodilator therapy for patients who have severe COPD, defined as FEV_1 <50% of predicted normal, and chronic bronchitis with two or more exacerbations in

the previous year (NICE TA461).[8] It is a phosphodiesterase-type-4 (PDE4) inhibitor and has been shown to reduce the rate of moderate or severe exacerbations in this population. However, roflumilast has a number of contraindications, including moderate to severe hepatic impairment, congestive heart failure or a history of depression associated with suicidal ideation or behaviour. It is also associated with a wide range of side-effects, with the most common including diarrhoea, nausea, weight loss, insomnia and depressive mood symptoms. The CS reported that these side-effects lead to discontinuation rates of approximately 30% in clinical trials and 70% in clinical practice, with the company estimating that only 5.4% of patients who were eligible for roflumilast in 2022 and 2023 actually received it. The EAG's clinical experts supported this view, reporting that very few (between 0 to 5%) of their patients with COPD are currently on long-term treatment with roflumilast, primarily due to issues with tolerability, particularly gastrointestinal side-effects.

2.3.3.3 Azithromycin

Azithromycin was included as a comparator in the NICE final scope, but was not presented as a comparator in the CS. The company justified the exclusion of azithromycin on the basis that it does not have a marketing authorisation for patients with COPD in England, and can therefore only be used as on off-label treatment for this group as recommended in the NICE guideline for COPD in over 16s.[7] There are a number of contraindications for azithromycin, including severe hepatic impairment, mild-moderate hepatic impairment, QT prolongation, bradycardia, cardiac arrhythmia or severe cardiac insufficiency, electrolyte disturbances and severe renal impairment, and myasthenia gravis. It is also associated with adverse events such as hearing loss and the development of antibiotic resistance. The EAG's clinical experts noted that, in clinical practice, azithromycin is only used as add-on therapy for a small, severe, subgroup of the patients who would be eligible for dupilumab (those who have ≥4 exacerbations per year). Some of the experts discussed how azithromycin might be considered as an additional treatment for people who were given dupilumab but continued to have exacerbations, but as it targets different symptoms, it would be unlikely to be considered as an alternative option. The EAG therefore considers the company's exclusion of azithromycin as a comparator to be reasonable and reflective of current NHS clinical practice.

2.3.4 Outcomes

The outcomes in the CS match those in the NICE final scope (see Table 11). Adjusted annualised rate of moderate or severe exacerbations was used as a marker of the incidence and severity of acute

exacerbations, and this was the primary outcome in both the BOREAS and NOTUS trials. The EAG's clinical experts confirmed that this was a key outcome in clinical practice when determining if a patient is responding to treatment.

Health-related quality of life was measured using the St George's Respiratory Questionnaire (SGRQ). The company reported that, while both trials also used the EQ-5D questionnaire, there was more limited data available than for the SGRQ. The BOREAS trial only recorded EQ-5D data at baseline, and while the NOTUS trial intended to collect EQ-5D data at baseline, week 24 and week 52, the early stopping criteria (see Section 3.2) meant that not all patients reached the 52-week time point, As a result, considerably less data was available at 52 weeks for the EQ-5D than the SGRQ. Although the SGRQ is validated in a COPD population, the company mapped the data to EQ-5D-5L outcomes to enable the data to be incorporated into the economic model. Although there is an established algorithm to allow for this type of mapping, the company reported that methodological limitations with the mapping study meant that it did not fully align with the baseline EQ-5D-5L data reported for BOREAS and NOTUS. Instead, the company developed their own mapping algorithm, the details and limitations of which are discussed in Section 4.2.9.1.

For safety outcomes, the company provided information on patients with treatment emergent adverse events (TEAEs), severe TEAEs, serious TEAEs and TEAEs specifically relating to dupilumab. The most common TEAEs were reported in the CS (Document B, Section B.2.10) and, in response to the EAG's clarification questions, the company provided the same information for serious and severe TEAEs.

The BOREAS and NOTUS trials both assessed the effectiveness and safety of dupilumab up to 52-weeks. As such, there is no information about the longer-term effects of dupilumab. However, the EAG's clinical experts stated that 52 weeks is an appropriate time over which to assess a patient's response to COPD treatment in clinical practice. The timepoints used to assess the outcomes therefore appear reasonable.

The EAG's clinical experts did not identify any additional outcomes or alternative assessment methods that would be more relevant to clinical practice. The outcomes reported in the BOREAS and NOTUS trials, and those selected by the company to address the NICE final scope, therefore appear appropriate to answer the decision problem.

2.3.5 *Subgroups*

Subgroups in the CS matched those in the NICE final scope (high EOS [≥500 cells/µL] and high FeNO [≥20 ppb]). No additional characteristics were identified by the EAG's clinical experts as likely to affect a patient's response to treatment and so the choice of subgroups appears reasonable.

3 Clinical effectiveness

3.1 Critique of the methods review

The company conducted a systematic literature review (SLR) to identify randomised controlled trials (RCTs), *post-hoc* analyses or pooled analyses of RCTs that compared the efficacy and safety of dupilumab or comparators in adults with uncontrolled, moderate to severe chronic obstructive pulmonary disease (COPD), with blood eosinophils (EOS) ≥300 cells/µL who were on triple therapy or double therapy if ICS was not appropriate.

Methods used for the SLR are summarised in Table 12. The EAG considers the methods used to be appropriate, and broader than specified in the NICE final scope. The SLR was updated in August 2024, three months prior to the submission, and so is unlikely to have missed any substantial, more recent, evidence.

Table 12. Summary of EAG's critique of the methods implemented by the company to identify evidence relevant this appraisal

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Data sources	CS Appendix D, Section D.1.1	**Appropriate** The following databases were searched: • MEDLINE • Embase • Cochrane CENTRAL • National Institutes of Health ClinicalTrials.gov • EU Clinical trials register • World Health Organization International Clinical Trials Registry Platform The following conference proceedings were searched: • International Conference of the American Thoracic Society • European Respiratory Society International Congress • Global Initiative for Chronic Obstructive Lung Disease (GOLD) International COPD Conference • CHEST Annual Meeting • International Workshop on Lung Health

		Manual searches were also performed using: • review articles • reference lists of full-text publications • free-text keyword searches using internet search engines
Search strategies	CS Appendix D, Section D.1.1	**Appropriate** Searches were broader than the decision problem and included the relevant population, interventions and study designs. The initial search was performed in December 2023, followed by an update search in August 2024. This was 3 months prior to submission and so the likelihood of missing key references appears low. The main trials in the CS were both identified in the SLR.
Inclusion criteria	CS Appendix D, Section D.1.2	**Appropriate** The population and intervention match those in the NICE final scope and decision problem. The included comparators were wider than the decision problem and outcomes were appropriate to meet those specified in the scope. The SLR therefore appears unlikely to have missed any relevant studies based on the inclusion criteria.
Screening	CS Appendix D, Section D.1.2	**Appropriate** Abstract and full-text screening was completed by two independent investigators, with discrepancies resolved by a third reviewer.
Data extraction	CS Appendix D, Section D.1.2	**Appropriate** Data was extracted by a single reviewer in an Excel-based data extraction workbook. All extracted data was validated by a second reviewer.
Tool for quality assessment of included study or studies	CS Appendix D, Section D.3	**Some concerns** The Cochrane Risk of Bias Assessment Tool 2.0 was used for quality assessment which is appropriate. However, explanations for the quality judgement for each domain were not provided. The EAG performed its own quality assessment of the key trials from the CS (BOREAS and NOTUS) and while it agrees with the assessment for BOREAS, there are some concerns about the interim analysis methods used in NOTUS which are not reflected in the company's risk of bias assessment.

Abbreviations: CS, company submission; EAG, External Assessment Group; NICE, National Institute for Health and Care Excellence; SLR, systematic literature review.

The SLR identified 2,388 records in the initial searches, with an additional 154 identified in the update search (Figure 1 and Figure 2, CS Appendix D). A total of 199 full-text articles were screened, with 17 identified as relevant. Four were *post-hoc* analyses of the BOREAS trial which did not provide additional information to previous publications and were excluded, leaving 13 publications included in the review. Of these, five were primary RCTs, three were *post-hoc* analyses of RCTs and five were pooled analyses of RCTs.

While 13 studies reported on treatment in the population specified in the decision problem, only seven included interventions relevant to the scope. These comprised four trials assessing two treatments:

- Dupilumab versus placebo:
  - BOREAS: One RCT and four *post-hoc* analyses;
  - NOTUS: One RCT.
- Roflumilast versus placebo:
  - One *post-hoc* pooled analyses of two trials (REACT and RE2SPOND).

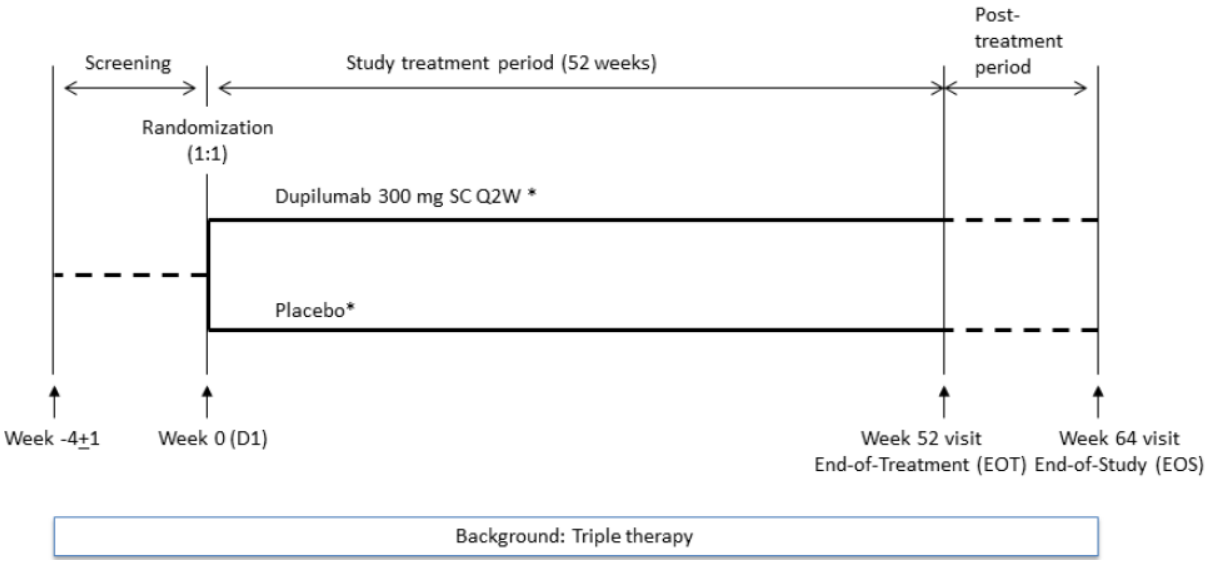
As discussed in Section 2.3.3.3, the company did not consider azithromycin a relevant comparator, but for completeness it was included in the list of interventions in the literature search. All evidence identified for azithromycin was excluded during screening, primarily for including a different population to the decision problem. This supports the company's statements about the lack of clinical evidence available for the use of azithromycin in the population proposed to be eligible for dupilumab.

Based on the available evidence, the EAG agrees that the direct evidence between dupilumab and placebo is the most appropriate against which to assess the effectiveness of dupilumab. The company performed ITCs for dupilumab and roflumilast but noted major concerns about the robustness of these analyses, based on differences in background treatment and disease severity. These concerns appear to be justified and are discussed in more detail in Section 3.3.5.

3.2 Critique of trials of the technology of interest

Two RCTs (BOREAS [NCT03930732] and NOTUS [NCT04456673]), both comparing dupilumab to standard of care without dupilumab, were the focus of this submission. Both were Phase III, placebo-controlled, double-blind, randomised multicentre trials, with participants randomised to either 300 mg dupilumab delivered subcutaneously once every two weeks (as specified in the marketing authorisation) or placebo (Figure 3). Each study also included a 12-week post-treatment period (weeks 52 to 64), where treatment was withdrawn, and patient responses were monitored. Results of this period are summarised in Section 3.3.5 to inform what may happen to patients who discontinue treatment.

Figure 3. Study design of the BOREAS and NOTUS trials. Reproduced from Figure 12 of the CS, Document B.



Abbreviations: Q2w, once every two weeks; SC, subcutaneous

Although both studies included a 52-week treatment phase, the design of NOTUS was modified to include an interim analysis, aimed at demonstrating the effectiveness of dupilumab when 92% of the information fraction for the primary endpoint was reached. This decision was made based on the statistically significant results from the multiplicity-controlled endpoints of the BOREAS trial. In NOTUS, the information fraction was reached once 681 participants had reached week 52, meaning that 21.3% of those in the trial did not reach the 52-week endpoint before the database lock. The stopping criteria for the trial was based on statistical significance of the primary endpoint (annualised rate of moderate or severe COPD exacerbations over 52 weeks of treatment), which the EAG's clinical experts considered one of the most important outcomes when assessing treatment effectiveness. A benefit of interim analysis is the ability to end trials early, thereby providing access to new treatments more quickly if the treatment is shown to be effective. This is useful in indications such as COPD, which the company noted is an area with high unmet clinical need. However, interim analyses can have drawbacks including the potential overestimation of treatment effects, which should be considered when interpreting the results of the NOTUS study.

The COVID-19 pandemic occurred during both the BOREAS and NOTUS trials (**Key issue 1** in Section 1.1), leading to several factors which should be considered when interpreting the results. These include:

- Changes to some of the methods of outcome assessment. The CS reports that on-site visits were replaced by telephone calls between weeks 16 and 62. This could impact on the quality and accuracy of outcome assessment.
- The effects of the COVID-19 pandemic on COPD outcomes. Research suggests that people with COPD had fewer exacerbations during the pandemic, which may be a result of shielding.[9] The EAG's clinical experts confirmed that, in their experience, people with COPD tended to shield more during the pandemic than other people. If the same is true of patients in the trials, then patients in the placebo arm may have had fewer exacerbations that they otherwise would, thereby underestimating the effects of dupilumab. However, if exacerbations in both groups were reduced to a similar extent, then the relative effects of treatment may not be affected.
- The effects that having a COVID-19 infection could have on patient outcomes. The statistical analysis plans for both trials state that subgroup analyses were planned if more than 10% of patients were impacted by COVID-19, but this threshold was not reached in either trial. However, the definition used in the trials (participants with any critical or major deviation related to COVID-19 or who permanently discontinued study intervention or study due to the COVID-19 pandemic or an AE of COVID-19) represents only those who were most severely affected by COVID-19. 9.0% of patients in the dupilumab arm and 8.8% of patients in the placebo arm reported treatment-emergent adverse events (TEAEs) due to COVID-19, and so it is important to consider whether this could have affected either the severity of their COPD, or their response to treatment.

The company provided additional information in response to the EAG's clarification questions concerning the effects of COVID-19 on trial design and outcomes. They reported that only 2.5% of total visits in the placebo arm and 2.1% of visits in the dupilumab arm were impacted by COVID-19, resulting in either a delay in the visit, or missing data either due to a visit being replaced by a phone call, or the use of a partial on-site visit. The percentage of visits that were impacted at each follow-up point ranged from 0.7% to 4.0%. Given that a relatively small proportion of visits were impacted by COVID-19, the EAG does not consider the effects of the pandemic likely to have had a major impact on outcome assessment.

The company also provided subgroup analyses for patients who reported TEAEs due to COVID-19 for three outcomes (annualised rate of moderate or severe COPD exacerbations, pre-bronchodilator FEV_1 and SGRQ score). Differences between dupilumab and placebo were smaller for patients who

reported TEAEs due to COVID-19 than those who did not. These results are discussed in more detail in Sections 3.3.1 to 3.3.4, but do not generally indicate a major impact of the inclusion of patients who reported adverse events relating to COVID-19.

The company reported that both trials were at low risk of bias (Table 23 in the CS). The EAG's quality assessment is presented in Table 13, and mostly aligns with the company's assessment. However, while the EAG considers BOREAS to be at low risk of bias, there are some concerns about the risk of bias in NOTUS, given the interim analysis methods discussed above.

Table 13. EAG's summary of the design, conduct and analysis of the BOREAS and NOTUS trials.

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Randomisation	• BOREAS statistical analysis plan – Section 1.1. • NOTUS statistical analysis plan – Section 1.1	**Appropriate** Participants were randomised using 1:1 randomisation. Randomisation was achieved using a permuted block randomisation schedule via Interactive Voice Response System/Interactive Web Response System, and patients were stratified by country and ICS dose.
Blinding and allocation concealment	N/A	**Appropriate** The study was double-blind with allocation to trial arms determined using an interactive voice/web-response system.
Eligibility criteria	CS Table 19	**Appropriate** The EAG's clinical experts agreed that the inclusion and exclusion criteria for BOREAS and NOTUS were appropriate. NOTUS expanded the upper age limit from 80 to 85 years during the trial, but this is not expected to impact on efficacy or safety outcomes.
Baseline characteristics	Appendix S, Table 1 and Table 2	**Appropriate** Both studies reported similar baseline characteristics between the dupilumab and placebo arms. There were some differences between studies for race (a greater percentage from an Asian population and a smaller percentage from American Indian/other Pacific Islander for BOREAS compared to NOTUS). A greater percentage had two exacerbations in the year prior to the trial in the NOTUS placebo arm than the BOREAS placebo arm, while fewer had three or more exacerbations. Other baseline characteristics were similar between trials. Once the trials were pooled, baseline characteristics were similar across trial arms.

Dropouts	NOTUS CSR and BOREAS CSR – Figure 2	**Appropriate** Dropouts were relatively low for both trials (between 4.9% to 6.6%) and similar across trial arms.
Statistical analysis		
Sample size and power	CS Table 21	**Appropriate** Both studies were designed to have >90% power to detect a 25% relative risk reduction in the primary endpoint, with 90% power at a 2-sided significance level of α=0.05.
Handling of missing data	CS Table 22. Clarification responses, A1.	**Appropriate** For event and time-to-event outcomes, data were censored at the time of discontinuation. For continuous outcomes, data were imputed using MMRM based on a missing at random assumption. Clarification responses from the company indicate that only a small proportion of assessments were not completed at 52 weeks and missing data did not have a notable impact on the results.
Outcome assessment	CS Table 19. Clarification responses, A5 and A6.	**Appropriate (BOREAS)** Clinical response outcomes were assessed using measures that are commonly used in practice. HRQoL was assessed using a validated tool. Although some visits were impacted due to COVID-19, the majority of visits were completed in line with the protocol. **Some concerns (NOTUS)** Interim analysis methods meant that 21.3% of patients did not reach the 52-week assessment point.

Abbreviations: CS, company submission; EAG, External Assessment Group; HRQoL, health-related quality of life; ICS, inhaled corticosteroids; MMRM, mixed modes for repeated measures

The matching trial design, population, interventions, comparators and outcomes meant that the company chose to pool the analysis of the two trials. Given the similar baseline characteristics between the two trials, the EAG considers this an acceptable approach for outcome assessment. The pooled baseline characteristics were similar between the dupilumab and placebo arms (Table 20, CS Document B), and the EAG's clinical experts considered them to be reflective of patients who would be eligible for dupilumab in clinical practice in England. As the pooled trials were the only evidence for dupilumab in this population, no meta-analysis was required.

3.3 Critique of the clinical effectiveness analysis and interpretation

A summary of the results of each individual trial are presented in the CS (Document B, Section B.2.6), while the sections below focus on the results of the pooled analysis, considering the effectiveness and safety of dupilumab compared to placebo.

The CS reports some of the differences between dupilumab and placebo to be clinically meaningful (**Key issue 2** in Section 1.1). In response to clarification questions, the company provided justification for the thresholds used to represent a clinically meaningful difference for each outcome (Table 14).

Table 14. Minimal clinically important differences (MCIDs) used for each outcome.

Outcome	Validated MCID?	Company justification for other MCID
COPD exacerbation rate	No	• Any statistically significant reduction between dupilumab and placebo may be considered clinically meaningful due to the serious consequences from exacerbations. • Other interventions that decrease exacerbation rates between 20%-25% are considered clinically significant and can be anchored to the SGRQ MCID of 4 points.[10]
Change in FEV_1	No Change of 100 ml has been proposed but not validated[11]	• Any statistically significant improvement in FEV_1 might be considered clinically significant in the context of a disease characterised by progressive lung function decline. • UK clinical expert opinion noted that a 100 mL or more improvement in FEV^1 would generally be considered clinically significant depending on the individual patient's starting point – a lower FEV_1 improvement (e.g., 50 mL) might still be clinically significant for a patient who's FEV_1 was already low.[12]
Health-related quality of life (SGRQ)	Yes Change ≥4 points[13]	• UK clinical expert opinion noted that quality of life improvement is hard to achieve with other medical interventions and so 2.0-2.5 point between-group differences may be clinically relevant.[14]
E-RS	No	• Empirically derived an anchor-based threshold of a 3.7 point improvement based on BOREAS data.

Abbreviations: COPD, Chronic obstructive pulmonary disease; E-RS, Evaluating Respiratory Symptoms; FEV_1, forced expiratory volume in 1 second; MCID, minimal clinically important difference; SGRQ, St George's Respiratory Questionnaire.

The EAG's clinical experts were not aware of any clinically meaningful differences that are commonly used in practice beyond those reported by the company. With the exception of SGRQ, the EAG did not identify any additional threshold that are considered validated MCIDs for COPD. The EAG's considerations in relation to the MCIDs outlined in Table 14, and their use in the discussion of the results in Section 3.3, are outlined below:

- COPD exacerbation rate: The assumption that any significant reduction in exacerbations is clinically meaningful could be reasonable, particularly as the population eligible for dupilumab already have severe, uncontrolled disease and, as indicated by the company, exacerbations can have serious consequences. However, the magnitude of the reduction should also be considered to assess whether this difference would be meaningful to a patient or have a substantial impact on the resources needed to treat exacerbations.

Both the company's suggested threshold and the magnitude of any benefit is considered as part of the EAG's discussion of the results.

- Change in FEV_1: The company reports that a change of 100 ml could be considered clinically meaningful, but that this may depend on an individual's disease severity. It should be noted that a value similar to this threshold (108.69 ml) has been used in the economic model to represent the annual decline in FEV_1 that is expected for people with EOS >300 cells/µl who have a COPD exacerbation (see Section 4.2.4.2). Without further evidence assessing the change required to represent a clinically meaningful difference in patients with uncontrolled COPD characterised by raised blood EOS, it is difficult to confidently use the 100 ml threshold to assess the effects of dupilumab in this population. Therefore, while this threshold will be considered in the EAG's discussion of the results, it is not used as the sole marker against which to determine a clinically meaningful difference between dupilumab and placebo.
- SGRQ: A change in SGRQ of 4 points has been validated as a method of assessing a clinically meaningful difference in health-related quality of life in patients with COPD.[13] Research presented by the company indicates that responder analysis (the number of patients who reported a change of 4 points or more) may be more valuable than the change in mean group score, and so this has been included as part of the EAG's discussion of the results.
- E-RS. There is limited information on how the 3.7 point threshold was established by the company, and so while this is noted in the EAG's discussion of the results, it is not used as the sole marker against which to determine a clinically meaningful difference. Evidence identified by the EAG, anchored to either change in SGRQ or change in Patient Global Rating in COPD severity, proposed that a change of 2 points could be considered clinically meaningful.[15, 16] However, this 2-point criterion does not appear to be used in clinical practice.

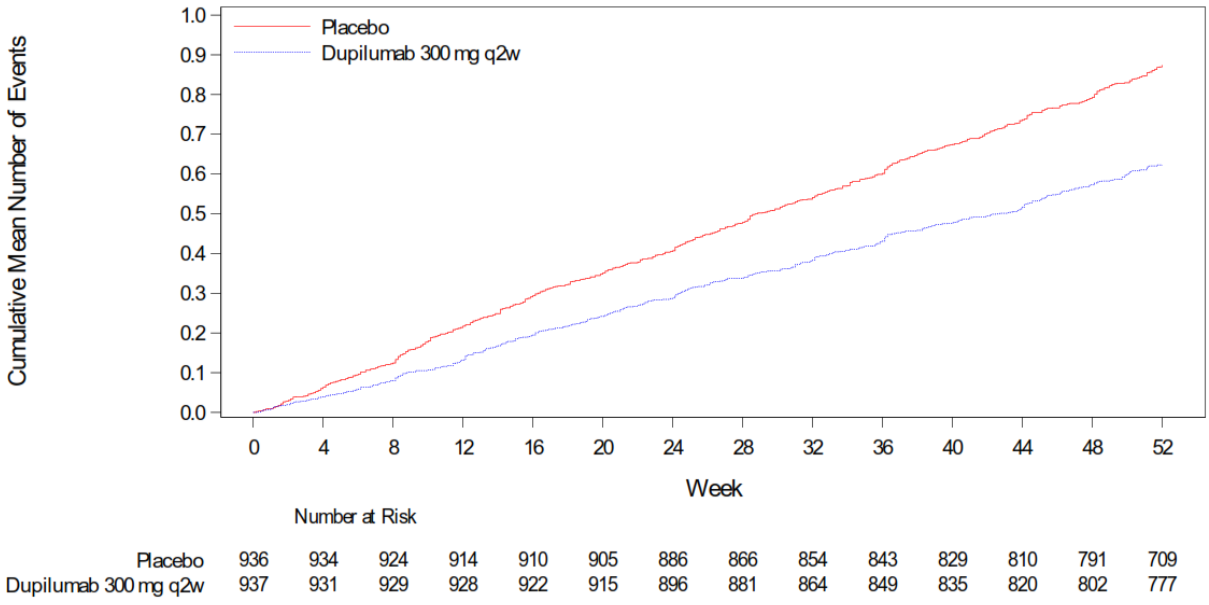
3.3.1 Primary outcome

The primary outcome for both trials was adjusted annualised rate of moderate or severe exacerbations. The annualised rate of exacerbations was significantly lower with dupilumab compared to placebo (rate ratio: 0.69; 95% CI: 0.60 to 0.79; p<0.0001), with a difference observed between trial arms from 4 weeks, which progressively increased until 52 weeks (Figure 4). The statistically significant difference between dupilumab and placebo met the company's threshold for

assuming a clinically meaningful difference between treatments (Table 14) (**Key issue 2** in Section 1.1). While the differences between treatments were statistically significant, the adjusted annualised rate of moderate or severe exacerbations per year was 0.79 (95% CI 0.69 to 0.92) for dupilumab compared to 1.16 (95% CI 1.01 to 1.33) for placebo, reflecting a difference of 0.37 exacerbations per patient per year. As such, while dupilumab appears to reduce the overall number of exacerbations in this group of patients, the effects for individual patients may be modest (on average, roughly the equivalent of one fewer exacerbation every three years).

The main difference between trial arms arose from the differences in moderate, rather than severe, exacerbations. This seems unsurprising, given that moderate exacerbations accounted for over 90% of the total exacerbations in each arm, with 505 moderate events reported for dupilumab compared to 698 for placebo (Table 25 of CS, Document B). With fewer severe exacerbations, differences between trial arms were less pronounced, with 54 severe events for dupilumab (approximately 0.06 exacerbations per patient) compared to 76 for placebo (0.08 exacerbations per patient).

Figure 4. Pooled analysis of the cumulative mean number of moderate or severe COPD exacerbations. Reproduced from Figure 13 of the CS, Document B.



Abbreviations: q2w, every two weeks.

Despite the interim analysis used for the NOTUS trial, a similar proportion of exacerbations were reported between the dupilumab and placebo arms as for the BOREAS trial. The cumulative mean number of moderate or severe exacerbations also followed a similar trend to BOREAS, suggesting

that the pooled analysis may not have been impacted by the early stopping criteria used in the NOTUS trial. The EAG therefore considers the pooled analysis to be an accurate reflection of the benefits of dupilumab compared to standard care for the rate of exacerbations over the 52-week treatment period.

When considering the effects of COVID-19 (**Key issue 1** in Section 1.1), the company reported a lower annualised rate of moderate or severe exacerbations for dupilumab compared to placebo in all patients regardless of whether they reported treatment emergent adverse events (TEAEs) relating to COVID-19. This difference was non-significant for patients who experienced a TEAE related to COVID-19, but significant for those who did not:

- TEAEs relating to COVID-19: rate ratio 0.86, 95% CI: 0.57 to 1.31; p=0.48;
- No TEAEs relating to COVID-19: rate ratio 0.67, 95% CI: 0.57 to 0.78; p<0.0001.

There are a number of potential causes of the different treatment effects between these groups, including an underlying effect of COVID-19, or the likelihood that people who had a COVID-19 infection would remain at home, reducing their exposure to other factors that could cause an exacerbation. However, the results for the non-COVID-19 subgroup are similar to those reported for the overall analysis, suggesting that COVID-19 may not have had a major impact on exacerbation outcomes in the trials. This reflects the company's findings from expert elicitation, where clinical experts stated that COPD exacerbations tend to be lower in trials than in clinical practice, and that the rates from BOREAS and NOTUS appear similar to those from trials published before the pandemic. As such, it appears that the results may be a reasonable representation of the impact of dupilumab on exacerbation rates outside of the COVID-19 pandemic.

3.3.2 Secondary outcomes

3.3.2.1 Key secondary endpoint

The key secondary endpoint was change in pre-BD FEV_1 from baseline to Week 12 and Week 52. Dupilumab resulted in significantly greater improvements in pre-BD FEV_1 than placebo at both timepoints, and while the absolute difference between trial arms was smaller at week 52 than week 12, both were statistically significant:

- Week 12 dupilumab vs placebo: LS mean difference: +83 ml; 95% CI: 53 to 112; p<0.0001;

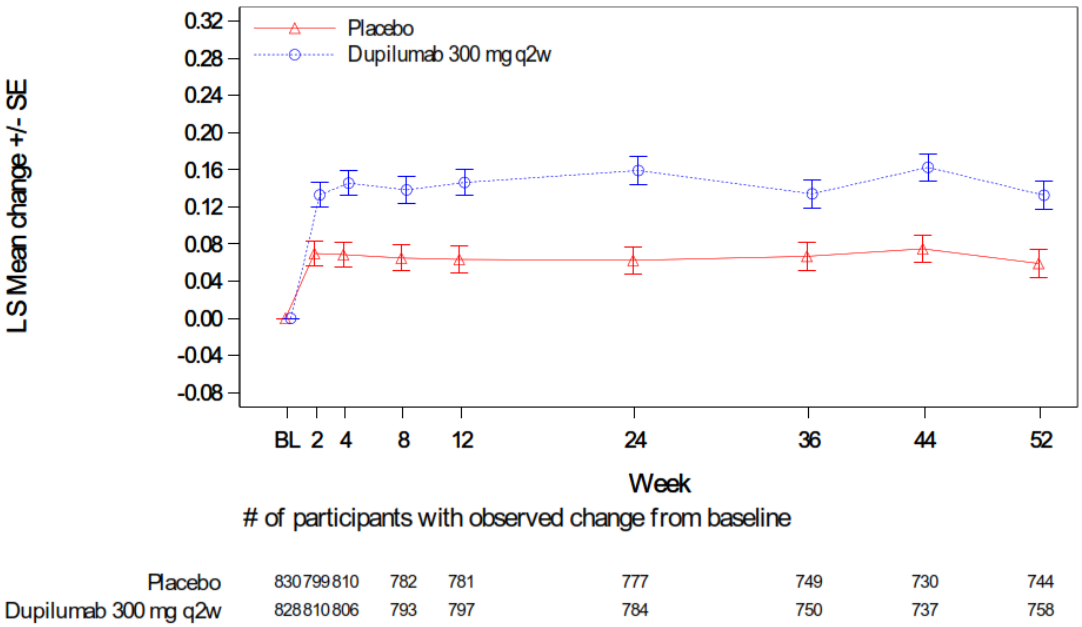
- Week 52 dupilumab vs placebo: LS mean difference: +73 ml; 95% CI: 40 to 107; p<0.0001.

The benefits of dupilumab appear to occur soon after the initiation of treatment, with differences between the treatment arms evident at two weeks and remaining relatively stable from this point onwards (Figure 5). Interestingly, an improvement in pre-BD FEV_1 was also seen during the first two weeks in the placebo arm. This may have resulted from the optimisation of background care, which is often seen during COPD trials where patients are monitored more closely than they would otherwise be in clinical practice (CS, Appendix P). However, although changes were evident in both arms, the change was greatest for patients in the dupilumab arm, indicating some benefits of dupilumab for improving pre-BD FEV_1.

The improvements with dupilumab compared to placebo meet part of the company's proposed threshold used to indicate a clinically meaningful difference (a statistically significant improvement, Table 14) (**Key issue 2** in Section 1.1). However, it does not meet the 100 ml threshold that the company reported has been suggested, but not validated, in the literature.[11] Given the lack of validation of this threshold, and the uncertainty about the relevance of the 100 ml threshold for different levels of COPD disease severity, it is therefore unclear whether this difference observed between dupilumab and placebo is clinically meaningful.

While the change in pre-BD FEV_1 was smaller in the NOTUS trial than BOREAS, both reported significantly greater improvements with dupilumab than placebo at 12 and 52 weeks, again supporting the use of the pooled analysis despite the interim analysis methods used in the NOTUS trial.

Figure 5. Pooled analysis of LS mean change from baseline in pre-BD FEV_1 (L) up to Week 52. Reproduced from Figure 14 of the CS, Document B.



Abbreviations: LS mean, least squares mean; Q2w, every two weeks; SE, standard error

As for the primary outcome, the COVID-19 subgroup analysis (**Key issue 1** in Section 1.1) for change in pre-BD FEV_1 from baseline to 52 weeks demonstrated a significant difference between dupilumab and placebo for patients who did not experience a TEAE related to COVID-19, compared to a non-significant difference for those who did:

- TEAEs relating to COVID-19: LS mean difference: +60 ml, 95% CI: -80 to 200; p=0.40;
- No TEAEs relating to COVID-19: LS mean difference +80 ml, 95% CI: 40 to 110; p<0.0001.

The smaller difference between treatments for the subgroup who reported TEAEs related to COVID-19 suggests that the inclusion of these patients could have led to an underestimation of the effects of dupilumab compared to placebo for the lung function outcomes. However, results for the subgroup who did not report effects of COVID-19 were similar to the results from the overall analysis, again meeting part of the company's threshold used to indicate a clinically meaningful difference (statistical significance). Consequently, the EAG considers that COVID-19 does not appear to have had a major impact on the lung function results from the two trials.

3.3.2.2 Other secondary endpoints

A range of endpoints were used to assess a patient's change in lung function from baseline, with each showing significantly greater improvements with dupilumab compared to placebo (Table 15). Forced expiratory volume and forced expiratory flow measures reflect the changes discussed above for the key secondary endpoint (change in pre-BD FEV_1 at 12 and 52 weeks), with significant improvements in all lung function outcomes seen soon after the start of treatment with dupilumab,

and differences between treatments remaining significant, and relatively stable, from approximately 4 weeks onwards (Figures 15 and 16 of CS, Document B). As with the key secondary endpoint, the difference in FEV_1 values between dupilumab and placebo met part of the company's threshold used to indicate a clinically meaningful difference (a statistically significant difference between treatments), but did not reach the additional 100 ml threshold (**Key issue 2** in Section 1.1). As such, there are uncertainties for all lung function measures when considering if the difference between treatments is clinically meaningful.

Table 15. Summary of other secondary endpoints (lung function measures)

Other secondary endpoints	LS mean difference: dupilumab vs placebo (95% CIs)	p value
Change in pre-BD FEV_1 from baseline		
2 weeks	+63 mL (34 to 92)	p<0.0001
52 weeks	+73 mL (40 to 107)	p<0.0001
Change in post-BD FEV_1 from baseline		
2 weeks	+57 mL (95% CIs not provided)	p=0.001
52 weeks	+74 mL (95% CIs not provided)	p<0.001
Change in pre-BD $FEF_{25-75\%}$ from baseline		
2 weeks	0.046 L/s (95% CIs not provided)	p=0.0014
52 weeks	0.051 L/s (95% CIs not provided)	p=0.0012

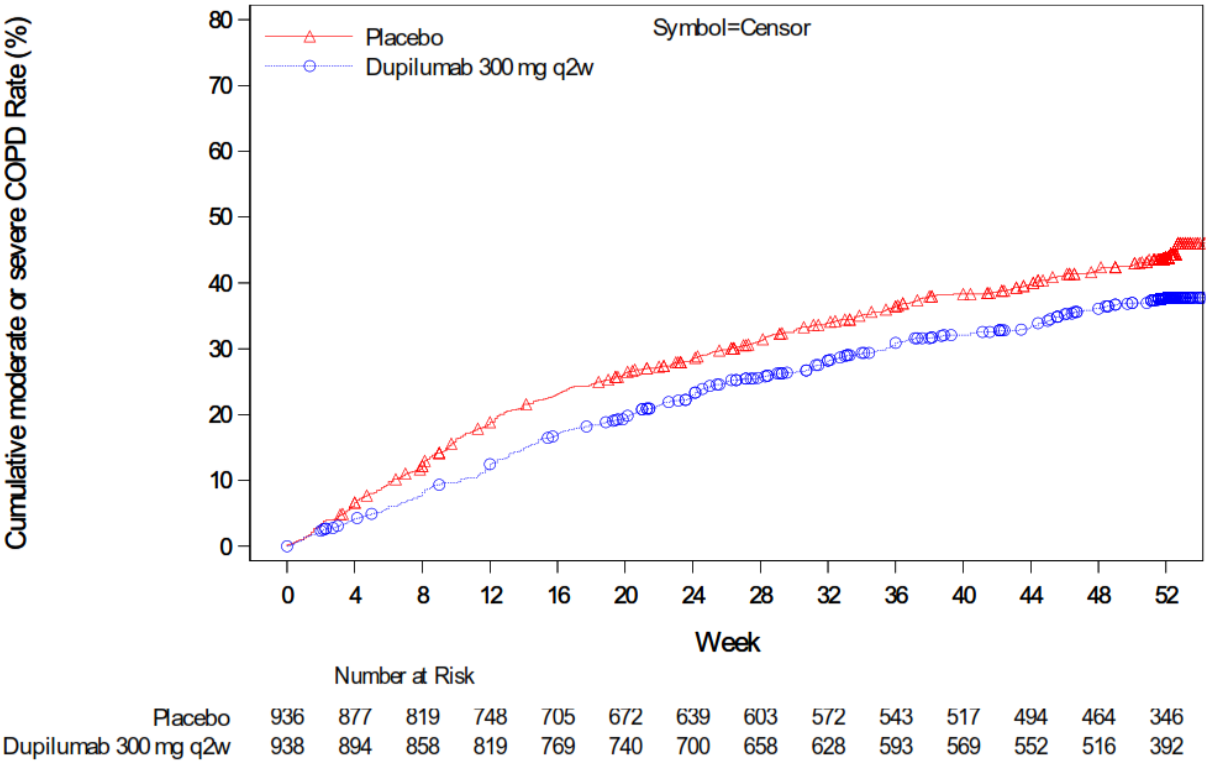
Abbreviations: BD, bronchodilator; CIs, confidence intervals; FEF, forced expiratory flow; FEV_1, forced expiratory volume in 1 second; L/s, litres per second; LS mean difference, least squares mean difference; mL, millilitres; pre-BD, pre-bronchodilator; post-BD, post-bronchodilator.

The incidence and severity of acute exacerbations (annualised rate of severe exacerbations over 52 weeks and time to first moderate or severe COPD exacerbation) were also reported as other secondary outcomes. Time to first moderate or severe COPD exacerbation was significantly longer with dupilumab than placebo (HR: 0.770; 95% CI: 0.666 to 0.892; p=0.0005), with benefits seen from week 4 which were sustained throughout the duration of the trial (Figure 6). These significant benefits were also seen when moderate or severe exacerbations were considered separately (severe exacerbations HR: 0.611; 95% CI 0.409 to 0.912; p=0.0160; moderate exacerbations rate ratio [redacted]).

Unlike the other exacerbation outcomes, differences between the trial arms for annualised rate of severe exacerbations were non-significant (rate ratio 0.674; 95% CIs 0.438 to 1.037; p=0.07). However, the rate was numerically lower for dupilumab than placebo, with 41 patients (4.4%) experiencing a severe exacerbation with dupilumab compared to 60 (6.4%) with placebo.

Information on the annualised rate of moderate exacerbations was provided in response to clarification questions. The difference between dupilumab and placebo was significant ([redacted]), meeting the company's criteria for a clinically meaningful difference (**Key issue 2** in Section 1.1). However, it should be noted that this reflected a difference of just [redacted] per patient per year, suggesting that the benefits of dupilumab experienced by individual patients may be relatively small.

Figure 6. Pooled analysis Kaplan-Meier plot of time to first moderate or severe COPD exacerbation event during the 52-week treatment period (pooled ITT population). Reproduced from Figure 17 of the CS, Document B.



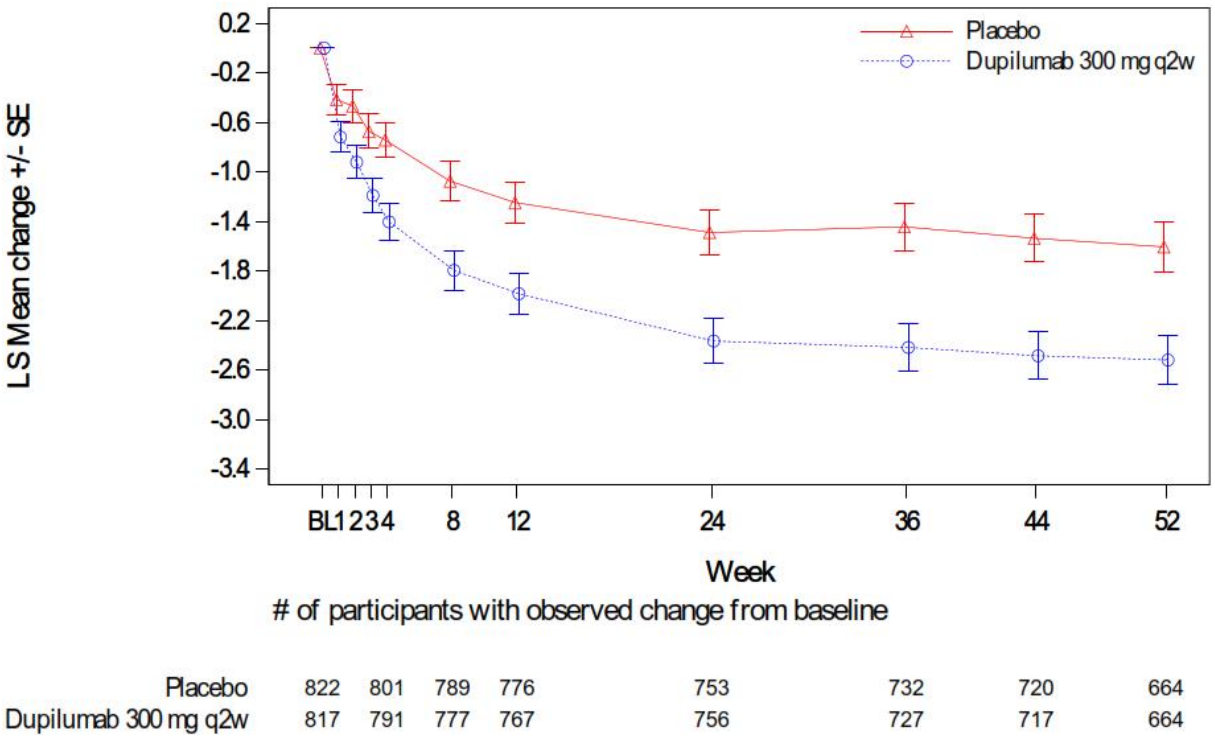
Abbreviations: COPD, chronic obstructive pulmonary disease; q2w, every two weeks.

3.3.2.3 *Exploratory endpoint*

The E-RS tool was used as a patient-reported measure of symptom control. The E-RS total score indicated greater improvements in symptom control with dupilumab than placebo from week 1 onwards (Figure 7), with the CS reporting statistically significantly greater improvements at both week 1 (LS mean difference vs placebo: −0.3; 95% CI: −0.6 to 0.0; p=0.0320) and week 52 (LS mean difference: −0.9; 95% CI: −1.4 to −0.4; p=0.0006). The difference in E-RS score between treatments did not reach the company's threshold for a minimal clinically important difference (3.7 points, Table 14) (**Key issue 2** in Section 1.1). However, as it is unclear how this threshold was determined, the EAG considers there to be uncertainty over whether this result is clinically meaningful.

The EAG notes that there was also a gradual reduction, albeit to a lesser extent than for dupilumab, in the E-RS score for the placebo arm (Figure 7). This may reflect the optimisation of background care, as discussed in Section 3.3.2.1, and indicates that the improvements in the dupilumab arm may reflect both the effects of dupilumab and the optimisation of care. It is therefore possible that the reduction in E-RS score seen in the trials may be greater than would be seen in clinical practice. However, as the relative improvements in symptom control were greater for dupilumab than placebo, the differences seen between dupilumab and placebo in the trials appear reasonable.

Figure 7. Pooled analysis LS mean change from baseline in E-RS: COPD total score up to Week 52 (pooled ITT population with an opportunity to reach Week 52). Reproduced from Figure 20 of the CS, Document B.



Abbreviations: BL, baseline; E-RS: COPD, Evaluating Respiratory Symptoms in COPD; ITT, intention-to-treat; LS mean, least squares mean; q2w, every two weeks; SE, standard error.

The E-RS subdomains (breathlessness, cough and sputum, and chest symptoms) each showed a similar decline in score from baseline to 52 weeks as reported for the total score (Table 16). Numerically greater changes were seen for the dupilumab than placebo arms, with the greatest difference evident for symptoms related to breathlessness.

Table 16. Change in subdomains of the E-RS tool from baseline to week 52. Reproduced from Table 53 of the company's clarification responses.

Week 52	Placebo (N=830)	Dupilumab (N=830)
Change (SD) from baseline in E-RS: COPD RS-Breathlessness up to week 52 visit	[redacted]	[redacted]
Change (SD) from baseline in E-RS: COPD RS-Cough and Sputum up to week 52 visit	[redacted]	[redacted]
Change (SD) from baseline in E-RS: COPD RS-Chest Symptoms up to week 52 visit	[redacted]	[redacted]

Abbreviations: E-RS: COPD, Evaluating Respiratory Symptoms in COPD tool; SD, standard deviation.

3.3.2.4 Additional analyses

The CS reports that dupilumab required 30% fewer systemic corticosteroid courses over the 52-week treatment period compared to placebo (relative risk: 0.701; 95% CI: 0.600 to 0.819; p<0.0001). The mean number of courses required per exacerbation were also provided following clarification questions (dupilumab mean 1.10 [SD 0.46]; placebo mean 1.16 [SD 0.53]). Comparison of these two outcomes indicates that, while dupilumab marginally reduces the number of courses required to treat each exacerbation, its main effect appears to be reducing the number of exacerbations, thereby reducing the overall number of systemic corticosteroids required to treat those exacerbations each year.

3.3.3 Quality of life

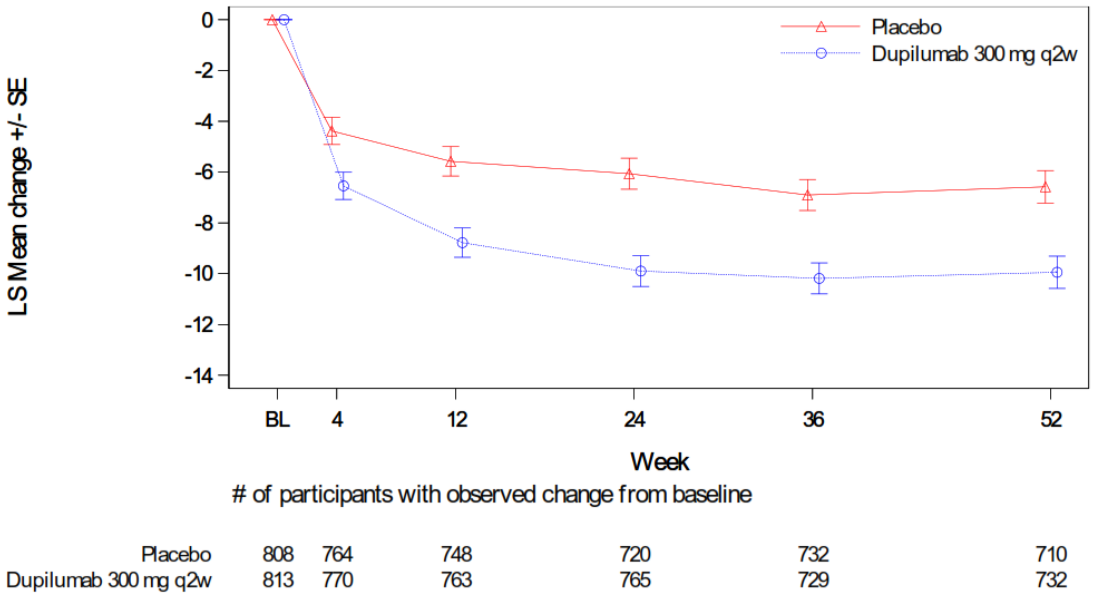
Health related quality of life (HRQoL) was measured using the Saint George's Respiratory Questionnaire (SGRQ) at baseline and week 4, then every 12 weeks until 52 weeks. While these results were the focus of the clinical analyses, the company mapped the SGRQ scores to the EQ-5D-5L for use in the economic model (see Section 4.2.9.1).

Greater improvements in HRQoL, reflected by a reduction in SGRQ score, were seen from week 4 onwards with dupilumab compared to placebo. The reduction from baseline was significantly greater for dupilumab than placebo at 52 weeks (LS mean difference: −3.4; 95% CI: −5.0 to −1.8; p<0.0001). Although significant, the difference between treatments did not reach the threshold of 4 points for a minimal clinically important difference (Table 14).

As noted for the change in E-RS score for symptom control, patients in the placebo arm also reported improvements in HRQoL (Figure 8). This may again reflect the optimisation of background care, but as for E-RS score, the greater relative improvements for dupilumab than placebo indicate that dupilumab is still likely to have some benefits for HRQoL over standard of care in clinical practice. The improvement in HRQoL in both arms is reflected by the percentage of patients that achieved a reduction in SGRQ score of ≥4 points (dupilumab 51.4%, placebo 44.6%; p=0.0089), although notably, while more patients achieved a clinically meaningful reduction in SGRQ score with

dupilumab than placebo, almost half of those in the dupilumab group did not report a clinically meaningful change in quality of life.

Figure 8. Pooled analysis LS mean change from baseline in SGRQ total score up to Week 52. Reproduced from Figure 19 of the CS, Document B.



Abbreviations: BL, baseline; ITT, intention-to-treat; LS mean, least squares mean; q2w, every two weeks; SE = standard error; SGRQ = St. George's Respiratory Questionnaire

Subgroup comparisons again highlighted the reduced impact of dupilumab for people who reported a TEAE related to COVID-19 (**Key issue 1** in Section 1.1):

- TEAEs relating to COVID-19: LS mean difference: -1.56, 95% CI: -6.60 to 3.47; p=0.54;
- No TEAEs relating to COVID-19: LS mean difference -3.59, 95% CI: -5.28 to -1.91; p<0.0001.

The difference between SGRQ score was greater for people who did not report any TEAEs relating to COVID-19 than those who did. However, the results for people who did not report any COVID-19 related TEAEs are similar to those for the overall analysis, suggesting a limited impact of COVID-19 on health-related quality of life outcomes in the study.

3.3.4 Safety

The CS presented information on treatment-emergent adverse events (TEAEs), serious TEAEs and severe TEAEs, the frequency of each of were similar between dupilumab and placebo (Table 17). TEAEs that occurred more frequently in one arm than the other were presented, defined as events

occurring in ≥2% of patients in one arm, and with a difference of ≥1% in comparison to the other arm. TEAEs that occurred more frequently with placebo than dupilumab were COPD (6.9% vs 5.3%) and hypertension (4.6% vs 3.4%). TEAEs that occurred more frequently with dupilumab than placebo were headache, back pain, urinary tract infection and gastritis (Table 32 of the CS, Document B). However, the differences in event frequency between arms were relatively small, with the greatest difference reported for back pain (4.5% for dupilumab vs 3.1% for placebo). The EAG therefore considers that the pooled results for TEAEs do not indicate any major safety concerns for dupilumab in comparison to current practice.

Table 17. Pooled safety outcomes. Reproduced from Table 31 of the CS, Document B.

	Dupilumab (n=938)	Placebo (n=934)
Participants with any TEAE, n (%)	676 (72.1)	663 (71.0)
Participants with any severe TEAE, n (%)	108 (11.5)	117 (12.5)
Participants with any treatment emergent SAE, n (%)	125 (13.3)	147 (15.7)
Participants with any TEAE leading to death, n (%)	19 (2.0)	15 (1.6)
Participants with any TEAE leading to permanent study intervention discontinuation, n (%)	32 (3.4)	28 (3.0)
Participants with any treatment emergent AESI, n (%)	79 (8.4)	76 (8.1)

Abbreviations: AESI, adverse event of special interest; SAE, serious adverse event; TEAE, treatment emergent adverse event.

Additional information on mortality was provided in response to clarification questions (Table 18). Of note is the higher number of deaths occurring in the dupilumab arm than with placebo. This stems mostly from the post-treatment period, and while this is a very small percentage of patients ([redacted]), the EAG considers this important to highlight, particularly as some of these deaths were a result of adverse events that occurred during the treatment period.

Table 18. Pooled mortality rates during the treatment and post-treatment phases of the trials. Reproduced from Table 18 of the clarification responses.

	Dupilumab (n=938)	Placebo (n=934)
Death on study	[redacted]	[redacted]
Death occurred during the TEAE period	[redacted]	[redacted]
Death occurred during post-treatment period	[redacted]	[redacted]
TEAE leading to death in the post-treatment period	[redacted]	[redacted]
Post-treatment AE leading to death in the post-treatment period	[redacted]	[redacted]

Abbreviations: AE, adverse event; TEAE, treatment emergent adverse event

While the pooled results do not highlight any major concerns for the safety profile of dupilumab compared to placebo, the interim analysis methods used in the NOTUS study should be considered when interpreting the results. Individual trial results highlight the greater number of patients experiencing adverse events in the BOREAS than NOTUS trial (Table 19). A lower percentage of TEAEs related to dupilumab were reported in the NOTUS trial (3.2%) than in BOREAS (7.5%), indicating that the pooled analysis may have underestimated the additional TEAEs associated with dupilumab. However, this may not be a major concern, given that while there is also a difference in the number of patients with any TEAE (Table 19), the relative difference between the dupilumab and placebo arms are similar for both trials. Therefore, while the pooled analysis may underestimate the number of adverse events experienced by this group of patients, the EAG considers that the relative effects of dupilumab compared to placebo are unlikely to be substantially different from those reported in the CS.

Table 19. TEAEs from the BOREAS and NOTUS studies.

	BOREAS		NOTUS	
	Dupilumab (n=469)	Placebo (n=470)	Dupilumab (n=469)	Placebo (n=464)
Participants with any TEAE, n (%)	363 (77.4)	357 (76.0)	313 (66.7)	306 (65.9)
Participants with any treatment emergent AESI, n (%)	40 (8.5)	43 (9.1)	39 (8.3)	33 (7.1)

Abbreviations: AESI, adverse event of special interest; TEAE, treatment emergent adverse event.

3.3.5 *Post-treatment outcomes*

Both the BOREAS and NOTUS trials included a 12-week post-treatment period, from weeks 52 to 64. [redacted] but in response to clarification questions, the company provided the post-treatment results [redacted] for exacerbations, pre-bronchodilator FEV_1, and SGRQ outcomes. Results were provided for:

- Patients who responded to dupilumab treatment ([redacted]): defined as either patients who had a lower rate of severe exacerbations while on treatment than prior to the study, those who had the same number of severe exacerbations as prior to the study but fewer moderate exacerbations, or those who had the same number of moderate or severe exacerbations as prior to the study;
- Patients who did not respond to dupilumab treatment ([redacted]): defined as patients who had more severe exacerbations while on treatment than prior to the study, or who had

the same number of severe exacerbations than prior to the study but more moderate exacerbations; and

- Patients in the placebo arm ([redacted]).

Results over the post-treatment period were similar for patients who were in the placebo arm and those classed as dupilumab responders. For placebo, [redacted] of patients experienced at least 1 moderate or severe exacerbation compared to [redacted] for dupilumab. The difference in unadjusted annualised moderate or severe exacerbation rate was also similar (Table 20), with a difference of only [redacted] for the post-treatment phase compared to [redacted] while on treatment. This suggests that the benefits of dupilumab appear to wane relatively quickly once treatment is stopped. While pre-bronchodilator FEV_1 remained relatively stable for the placebo patients in the post-treatment phase, a decline was seen in the dupilumab arm (Table 20). Dupilumab responders still showed a greater improvement in FEV_1 compared to baseline than patients in the placebo group, but this difference was smaller than at week 52. SGRQ scores were relatively stable for the placebo group between week 52 and week 64, while scores increased for dupilumab responders (reflecting lower HRQoL). As a result, SGRQ scores, and therefore HRQoL, was similar for the placebo and dupilumab groups by the end of the post-treatment phase (Table 20).

Table 20. Outcomes from [redacted] following the post-treatment phase (weeks 52-64).

	Placebo (n=440)	Dupilumab responders (n=426)
Exacerbations		
Participants experiencing at least 1 moderate or severe exacerbation, n (%)	[redacted]	[redacted]
Unadjusted annualised moderate or severe exacerbation event rate	[redacted]	[redacted]
FEV_1 change from baseline (L)		
Week 52, mean (SD)	[redacted]	[redacted]
Week 62, mean (SD)	[redacted]	[redacted]
SGRQ change from baseline		
Week 52, mean (SD)	[redacted]	[redacted]
Week 62, mean (SD)	[redacted]	[redacted]

Abbreviations: FEV_1, forced expiratory volume in 1 second; SGRQ, St George's Respiratory Questionnaire.

Results from the post-treatment phase indicate that the benefits of dupilumab wane relatively quickly once treatment is stopped. The company acknowledged that this is expected, given that dupilumab has a half-life of approximately 17 to 20 days and the median time to non-detectable

concentrations is between 10 and 11 weeks. This supports the views of the EAG's clinical experts that, if a patient shows a response to dupilumab treatment, they would expect them to remain on treatment beyond the 52 week assessment point. Without this, it appears that any benefits gained by the patient from the use of dupilumab would quickly be lost.

3.3.6 Subgroups

Results for the subgroups specified in the NICE final scope (high EOS [≥500 cells/µL] and high FeNO [≥20 ppb]) were reported for annualised rate of moderate or severe exacerbations and change in pre-BD FEV_1 at week 12. For both EOS subgroups, results favoured dupilumab for annualised rate of moderate or severe exacerbations (Table 21), with the greatest effect seen in the ≥500 cells/µl subgroup. The CS reports that the treatment effect in all subgroups was statistically significant, meeting the company's criteria for a clinically meaningful difference, although p values were not reported. Results for both EOS subgroups also favoured dupilumab for change in pre-BD FEV_1. Again, both were reported to be statistically significant, with the effect estimate for the ≥500 cells/µl subgroup exceeding the 100 ml value suggested by the company to indicate a clinically meaningful difference. However, as with the overall analysis, the lack of validation of the 100 ml value means it is difficult to conclude whether this difference was clinically meaningful.

When results were separated by baseline FeNO, results for both subgroups again favoured dupilumab (Table 21), with the greatest benefits seen in the ≥20 ppb subgroup for both outcomes. While the change in pre-BD FEV_1 exceeded the company's 100 ml threshold for a clinically meaningful difference in the ≥20 ppb subgroup, the threshold was not reached in the <20 ppb subgroup. Consequently, while patients in all subgroups appear to experience some degree of benefit with dupilumab compared to placebo, the greatest benefits are seen for those with higher blood EOS or higher FeNO.

Table 21. Subgroup outcomes for EOS at screening and baseline FeNO.

	n placebo	n dupilumab	Effect estimate (95% CI)
Annualised rate of moderate or severe COPD exacerbations (RR<1 favours dupilumab)			
EOS <500 cells/µl at screening	588	595	0.723 (0.608 to 0.860)
EOS ≥500 cells/µl at screening	348	342	0.600 (0.464 to 0.776)
Baseline FeNO <20 ppb	494	495	0.824 (0.680 to 1.000)
Baseline FeNO ≥20 ppb	371	367	0.552 (0.434 to 0.701)
Change in pre-BD FEV_1 at Week 12 (LS Mean difference >0 favours dupilumab)			
EOS <500 cells/µl at screening	583	589	57 (22 to 91)

EOS ≥500 cells/µl at screening	347	340	130 (76 to 184)
Baseline FeNO <20 ppb	492	491	58 (24 to 91)
Baseline FeNO ≥20 ppb	368	365	131 (74 to 187)

Abbreviations: COPD; Chronic obstructive pulmonary disease; EOS, eosinophils; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; LS mean difference, least squares mean difference; ppb, parts per billion

3.4 Critique of the indirect comparison

No direct comparisons were available between roflumilast and dupilumab for patients with COPD and blood EOS ≥300 cells/µl. However, the company's systematic literature review identified two trials (REACT and RE2SPOND), which provide evidence for roflumilast in patients with COPD. Neither trial used blood EOS count as an inclusion criterion, nor provided subgroup analyses for patients with raised blood EOS. Instead, a later analysis (Martinez *et al.* 2018) used data from the two trials to provide a pooled *post-hoc* analysis of the effectiveness of roflumilast in people with EOS ≥300 cells/µl.[17] The company noted that this was the only available evidence on which to base an ITC between dupilumab and roflumilast in the population that would be eligible for dupilumab.

While the Martinez *et al.* 2018 *post-hoc* analysis provides evidence for roflumilast in the relevant population, the CS highlights key differences between the REACT and RE2SPOND trials and the BOREAS and NOTUS trials, which the company suggest limits the ability to provide a robust ITC between the two treatments (**Key issue 3** in Section 1.1). Key differences identified by the company were:

- Differences in background therapies: 42% of patients in REACT and RE2SPOND were given triple therapy, compared to 98% in BOREAS and NOTUS; and
- Differences in disease severity: Only patients with severe or very severe COPD were included in REACT and RE2SPOND, compared to patients with moderate or severe COPD in BOREAS and NOTUS.

To address their concerns over background therapies, the company used a targeted literature review to examine the differences in the effects of double and triple therapy on annualised rates of moderate or severe exacerbations (CS, Appendix T). The meta-analysis of six studies showed benefits of triple therapy over double therapy for people with either high blood EOS or severe COPD (RR 0.84; 95% CI 0.81 to 0.88), which the company considered to provide support to their statements about the lack of similarity between the dupilumab and roflumilast studies. The EAG notes that one study in the literature review reported on a population with both high blood EOS and severe COPD

(most similar to the population proposed for dupilumab). While the effect estimate from this study numerically favoured triple therapy over double therapy, it was associated with wide 95% CIs (RR 0.80; 95% CIs 0.47 to 1.36), making it difficult to confidently draw robust conclusions on the comparative effectiveness of the two types of inhaled therapy.

When addressing differences in disease severity, the company noted that patients with very severe COPD could not be excluded from the roflumilast analyses, as the Martinez *et al.* 2018 study did not stratify the EOS subgroups by COPD severity. Instead, to align the dupliumab trials more closely with the REACT trial, the populations in the dupilumab trials were restricted by other characteristics, including FEV_1, smoking status and number of prior exacerbations. However, while this adjusted for some of the differences between trials, it could not remove the differences in background therapies or disease severity, both of which may impact a patient's response to treatment.

An additional concern raised by the company was that neither of the roflumilast studies included blood EOS count as a stratification factor at randomisation. As such, the *post-hoc* analysis of Martinez *et al.* 2018 was considered to have broken randomisation. The population restrictions used to align the dupilumab trials with those for roflumilast also required a breaking of randomisation. Baseline characteristics of the dupilumab trials following these adjustments were not provided, and so it is not possible to determine the effects of the restrictions on the populations in the dupilumab and placebo arms. Concerns over breaking of randomisation therefore add additional uncertainties when comparing dupilumab and roflumilast.

Given the differences outlined above, the company did not think that the patients in each trial were sufficiently similar to allow for a robust indirect treatment comparison (ITC) between dupilumab and roflumilast. Despite this, Bucher ITCs were produced to provide the information specified in the NICE final scope. However, the company emphasised that results were limited and not considered to be robust (Section B.2.9 of the CS, Document B).

The EAG agrees that the differences outlined above result in a high degree of uncertainty when interpreting the results of the ITC. There are also concerns about the appropriateness of the data for the analysis, given that Bucher ITC is designed to preserve randomisation across trials, but both the Martinez *et al.* 2018 study and the company's restriction of BOREAS and NOTUS resulted in the breaking of randomisation. The EAG notes that the use of a MAIC, rather than a Bucher's ITC, could have addressed some of the population differences with fewer methodological concerns. However,

the MAIC would be subject to the same concerns about the differences in trial populations as those highlighted for the Bucher's ITC, and requires a further breaking of randomisation when performing the weighting adjustments needed to match the populations between the trials of interest. It would therefore leave similar uncertainties when interpreting the results. The EAG therefore considers that the results of any ITC between dupilumab and roflumilast would be associated with substantial uncertainty.

An additional consideration for comparisons between dupilumab and roflumilast is the very limited use of roflumilast in current practice (see Section 2.3.3.2), and the limited overlap between the populations who would be considered for both treatments. The EAG's clinical experts highlighted how there are currently no further treatment options for many of the patients who would be eligible for dupilumab. As such, the EAG considers the direct evidence comparing dupilumab to placebo (the BOREAS and NOTUS trials), to be the most relevant for this appraisal. The EAG's critique therefore focuses on the direct pooled analysis of BOREAS and NOTUS and does not provide an assessment of the results of the ITCs.

3.5 Conclusions of the clinical effectiveness section

The EAG considers that the evidence provided by the company is appropriate to answer the decision problem, and any differences between the NICE final scope and the CS are justified (Section 2.3). The SLR was performed using appropriate methods and is likely to have identified the most relevant and current evidence (Section 3.1).

While the NICE final scope proposed azithromycin as a comparator, the company chose not to include it as part of their analysis. This decision was based on the limited overlap between the populations who would be eligible for dupilumab and azithromycin, the high number of contraindications and adverse events associated with azithromycin, and it's off-label use as a treatment for COPD. The EAG's clinical experts supported these statements, stating that the two treatments are used for different symptoms and, as such, while some patients might be eligible for both treatments, azithromycin would not be considered an alternative option to dupilumab. The company's exclusion of azithromycin as a comparator therefore appears reasonable.

Two trials provided direct comparisons between dupilumab with background therapy and placebo with background therapy. Of these, the EAG considers BOREAS to be at low risk of bias and NOTUS to be at moderate risk of bias due to the interim analysis methods used. However, comparisons of

the results from the trials indicate that the interim analysis was unlikely to have a substantial impact on the results, particularly for the effectiveness outcomes (Section 3.3). As such, the use of a pooled analysis for all outcomes appears appropriate.

Clinical effectiveness results for the comparisons between dupilumab and placebo indicate statistically significant reductions in moderate or severe exacerbations with dupilumab, with the greatest effect seen for moderate exacerbations. Dupilumab also resulted in statistically significant improvements in other lung function outcomes (pre- and post-bronchodilator FEV_1, incidence, severity and time to first exacerbation), symptom control and health-related quality of life with dupilumab (Section 3.3). However, there are uncertainties over whether these improvements represent a clinically meaningful improvement for dupilumab over placebo. For instance, while annualised rate of moderate or severe exacerbations (the primary outcome) indicated significantly fewer exacerbations with dupilumab, the difference in the number of exacerbations per patient per year was small. In addition, while most results were statistically significant, the differences between dupilumab and placebo did not meet the additional thresholds suggested by the company to indicate a clinically meaningful difference. However, only one of these thresholds (change in SGRQ score) is validated, leaving uncertainties about whether the results reflect a meaningful improvement with dupilumab.

An important area of uncertainty to note is the effect of dupilumab on severe exacerbations. The trials were not powered to detect differences in this outcome, making it difficult to determine the effect of dupilumab on the severe exacerbation rate. As severe exacerbations are a key driver of the cost-effectiveness in the company's analysis, due to the impact on costs, quality of life and mortality, this is a key uncertainty in the appraisal (see Section 4.2.5 for further discussion).

Safety outcomes showed little difference between dupilumab and placebo (Section 3.3.4). TEAEs that occurred more frequently with dupilumab than placebo were headache, back pain, urinary tract infection and gastritis, but the difference between treatments were relatively small. The EAG notes that, while small, there were more deaths in the dupilumab than placebo arm, some of which were a result of TEAEs (Section 3.3.4).

Effectiveness and safety outcomes were also provided for the post-treatment period (weeks 52-64) when treatment was withdrawn (Section 3.3.5). By the end of the post-treatment period, outcomes

were similar between the dupilumab and placebo groups, indicating that any benefits of dupilumab wane quickly once treatment is stopped.

In the absence of direct comparisons between dupilumab and roflumilast, the company produced ITCs using data from two RCTs which compared roflumilast to placebo (Section 3.4). However, the CS highlighted a number of differences between the trials, including disease severity and background therapies, which they believed would affect the robustness of the ITCs. Despite the company's attempts to align the populations of the dupilumab and roflumilast trials, key differences remained between the trials. This, in addition to concerns about the breaking of randomisation, means the EAG considers there to be substantial uncertainty associated with the results of the ITCs. Based on these concerns and the limited use of roflumilast in clinical practice, the EAG considers the direct evidence between dupilumab and placebo to be the most relevant for this appraisal and agrees with the exclusion of roflumilast as a comparator in the economic analysis.

An additional consideration when interpreting the results is the timing of the trials, both of which coincided with the COVID-19 pandemic (Section 3.2). Subgroup analysis suggests that COVID-19 may not have had a major impact on the overall outcomes, but it does add a degree of uncertainty which should be acknowledged when interpreting the results of the BOREAS and NOTUS trials.

4 Cost effectiveness

Table 22 below presents the incremental cost-effectiveness results of the company's updated (i.e., post clarification) base case. Results presented in this document are inclusive of a [redacted]% patient access scheme (PAS) discount for dupilumab, representing a price of [redacted] per pack.

Table 22. Updated (post clarification) company's base case results

Interventions	Total Costs (£)	Total LY	Total QALYs	Δcosts (£)	ΔLYs	Δ QALYs	ICER (£/QALY)
Deterministic results							
Background Therapy	[redacted]	[redacted]	[redacted]	-	-	-	-
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25,515
Probabilistic results							
Background Therapy	[redacted]	[redacted]	[redacted]	-	-	-	
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	23,624

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

4.1 EAG comment on the company's review of cost effectiveness evidence

In March 2024, the company conducted three systematic literature reviews (SLRs) to identify existing evidence on cost-effectiveness, health-related quality of life (HRQoL), and resource use and costs for treatments in patients with moderate to severe chronic obstructive pulmonary disease (COPD). Updated searches were performed in August 2024. A summary of the External Assessment Group's (EAG's) critique of the methods implemented by the company to identify relevant evidence is presented in Table 23. The EAG notes that the company designed its search strategy to identify studies published after January 2017 to build upon the evidence included in the NICE guideline for COPD (NG115), which the EAG considers is appropriate.[7]

The company also performed grey literature searches and hand searching to identify relevant evidence, such as conference abstracts and health technology appraisals (HTAs) published after 2020.

Table 23. EAG's critique of company's systematic literature review

Systematic review step	Section of CS in which methods are reported			EAG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Search strategy	Appendix G.1	Appendix H.1	Appendix I.1	Appropriate
Inclusion/ exclusion criteria	Appendix G.1	Appendix H.1	Appendix I.1	Appropriate
Screening	Appendix G.2	Appendix H.2	Appendix I.2	Appropriate
Data extraction	Appendix G.3	Appendix H.3	Appendix I.3	Appropriate

Quality assessment of included studies	Appendix G.4	Appendix H.4.3	Appendix I.4.3	The Drummond checklist[18] was used to assess the quality of cost-effectiveness studies. However, no quality assessment was performed for HRQoL and resource use and cost studies. The EAG considers that quality assessment should have been performed for all evidence. However, HRQoL data used in the cost-effectiveness analysis is derived directly from the BOREAS trial and no relevant cost data for use in the model was identified by the SLR.

Abbreviations: CS, company submission; EAG, External Assessment Group; HRQoL, health related quality of life; SLR, systematic literature review

In total (original search and August 2024 update), the SLRs identified a total of 599 cost-effectiveness records, 4,370 HRQoL records and 1,587 resource use and cost records. Following title/ abstract and full text screening, the company included 42 cost-effectiveness records (six records were identified through hand searching), 11 HRQoL records and 93 resource use and cost records. Appendix G of the CS describes the economic evaluations identified by the SLR, Appendix H presents the HRQoL evidence and Appendix I describes the resource use and cost evidence identified by the SLRs.

From the SLR, 35 unique economic evaluations were identified of which 17 were based on the GALAXY model (a regression-based model developed to assess the cost-effectiveness of inhaled treatments), 11 used Markov, semi-Markov and decision tree combined with Markov structures, one used a patient-level microsimulation and one used both the GALAXY model and decision tree plus Markov model. One study did not report the model structure used. The model structures of the economic evaluations identified in the SLR were used to inform the model structure for the company's *de novo* cost-effectiveness analysis.

The company considered the GALAXY model and a Markov structure to inform their *de novo* cost-effectiveness analysis. The company explained that replicating the GALAXY model was challenging as source code was not published. Instead, a Markov model approach was deemed appropriate as this structure was used in NG115, and the company's clinical experts endorsed the approach. Model structure is discussed further in Section 4.2.3.

The company considered that none of the included HRQoL studies reported UK-specific utility values and resource use by severity for use in the economic model. However, the company used published utility values to conduct scenario analysis (described further in Section 4.2.9) but these studies were not identified in the SLR. The EAG queried this with the company, who explained that because no UK-specific utility data were identified by the SLR, they considered evidence published prior to January 2017 and found one study that was used in NG115 (Rutten van Molken *et al*.,2006),[7, 19] and two studies that were identified through targeted searches of COPD models (Spencer *et al*., 2005 and Borg *et al*., 2004).[20, 21]

Overall, the EAG considers the company's SLR was thorough and comprehensive. The EAG notes that oral therapies were excluded from the SLR, despite roflumilast being listed in the NICE final scope.[22] However, in their clarification response, the company explained that oral therapies were only excluded from the cost-effectiveness SLR as they considered oral therapies were not relevant for the cost-effectiveness. However, the company did conduct hand-searches for inputs relevant for roflumilast. The exclusion of roflumilast as a comparator is discussed further in Section 2.3.3.2 and 4.2.2, but generally the EAG agrees with the company's base case approach.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 24 summarises the EAG's assessment of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in Section 2.3.

Table 24. NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Adheres to the NICE reference case.
Perspective on costs	NHS and PSS	Adheres to the NICE reference case.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Adheres to the NICE reference case.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Lifetime. Adheres to the NICE reference case.

Synthesis of evidence on health effects	Based on systematic review	Adheres to the NICE reference case.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	SGRQ data collected in the pooled BOREAS and NOTUS trials was mapped to EQ-5D-5L data, the cross-walked to EQ-5D-3L using the algorithm published by Hernández Alava *et al.* 2022,[23] as per the NICE health technology evaluation manual.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	SGRQ data and EQ-5D-5L used for mapping study was reported directly form patients.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Patients in BOREAS and NOTUS are generally representative of the UK patient population.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Adheres to the NICE reference case.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Adheres to the NICE reference case.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Adheres to the NICE reference case.

Abbreviations: EAG, External Assessment Group; NHS, national health service; NICE, National Institute for Health and Care Excellence; PSS, personal social services; QALY, quality adjusted life year; SGRQ, St. George's Respiratory Questionnaire; UK, United Kingdom

4.2.2 Intervention and comparator

As noted in Section 2.3.2, the intervention evaluated in the economic model is dupilumab in combination with background therapy. Dupilumab is given at a dose of 300mg subcutaneous injection every two weeks.

The comparator in the economic model is background therapy only. As previously described, background therapy consists of a combination of triple therapy (long-acting beta2- agonist [LABA] + long-acting muscarinic antagonist [LAMA] + inhaled corticosteroid [ICS]) or double therapy (LABA + LAMA) for those patients for whom ICS is not appropriate. The EAG notes that in the economic model, 100% of patients receive triple therapy as background therapy treatment, despite a small proportion of patients in pooled BOREUS and NOTUS receiving double therapy only. The company stated that clinical experts noted that the proportion of patients contraindicated to ICS is extremely

rare. As triple therapy is consistent in both arms of the economic model, 100% triple therapy was applied for simplicity.

Due to variability in prescribing practices for inhaled therapies in the UK, the company used a weighted basket approach for costing background therapy, based on market share data from IQVIA's Hospital Pharmacy Audit (HPA) 2023, as shown below in Table 25. The EAG's clinical experts agreed with the background therapies and market shares included.

Table 25. Background therapies included and corresponding market shares, reproduced from Table 38 of CS

Background therapies	Administration regimen	Market share
Trelegy Ellipta (fluticasone/umeclidinium/vilanterol)	1 inhalation daily	38.0%
Trimbow NEXThaler (beclomethasone/formoterol/glycopyrronium)	2 inhalations twice daily	59.4%
Trimbow (beclomethasone/formoterol/glycopyrronium)	2 inhalations twice daily	
Trixeo aerosphere (budesonide/formoterol/glycopyrronium)	2 inhalations twice daily	2.6%

As previously discussed in Section 2.3.3, both roflumilast and azithromycin were not included as relevant comparators by the company, despite being in the final NICE scope. Based on discussion with clinical experts and review of the data available, the EAG agreed with the company's exclusion of these two comparators. A scenario analysis was included by the company using roflumilast as a comparator, which the company state should be seen as highly exploratory with high uncertainty. The EAG agree that due to a lack of robust evidence to conduct an appropriate comparator analysis, the presented results are extremely uncertain and unsuitable for decision-making.

4.2.3 Modelling approach and model structure

The company produced a cohort-level short-term decision tree leading to a Markov state transition model, programmed in Microsoft Excel®. The analysis was carried out from an NHS and Personal Social Services (PSS) perspective. Costs and health effects are discounted at an annual rate of 3.5%, in line with the NICE Reference Case.[24]

4.2.3.1 Short-term decision tree

The short-term decision tree reflects the trial period of 52-weeks. Based on pooled intention-to-treat (ITT) data from both the NOTUS and BOREAS trials, patients are assigned to one of four health states at the end of the decision tree based on severity of COPD observed at the end of the trial

period in each treatment arm. COPD severity is measured by percent predicted forced expiratory volume ($ppFEV_1$) and classified in line with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria as detailed below:

1. GOLD stage 1: mild COPD, $ppFEV_1 \geq 80$,
2. GOLD stage 2: moderate COPD, $ppFEV_1 \geq 50$ and <80,
3. GOLD stage 3: severe COPD, $ppFEV_1 \geq 30$ and <50,
4. GOLD stage 4: very severe COPD, $ppFEV_1 < 30$.

The starting distribution of patients in each COPD severity health state is based on the average outcomes observed across the pooled BOREAS and NOTUS trials for both treatment arms combined. The company's original submission and model had used the incorrect starting distribution of patients. These were amended by the company during clarifications, with the updated proportions shown in Table 26. During clarification, the company also provided the option to use treatment arm specific baseline distributions in the model. This had a negligible impact on the ICER.

The EAG notes that although the population of interest for dupilumab is patients with uncontrolled COPD characterised by raised blood eosinophils (EOS), 1.9% were classified as mild at baseline.

Table 26. Baseline distribution of patients by COPD severity stage at start of decision tree

COPD severity health state			
Mild	**Moderate**	**Severe**	**Very Severe**
1.9%	47.9%	47.6%	2.5%

Abbreviations: COPD, chronic obstructive pulmonary disease

In the base case analysis, due to an initial increase in patients FEV_1 observed during the first 2 weeks of the trial, which appeared to be maintained until the end of the 52-week trial period, the company used ITT data for each treatment arm at both 2 and 52 weeks for the distribution across COPD severity health states during the decision tree. This was used in the estimation of life years during the decision tree period of the model.

Patients who did not respond to treatment during the 52-week trial period were classed as non-responders at the end of the decision-tree period and have outcomes comparable to background therapy only moving forward, as shown in Figure 9. The non-response criteria were developed based on discussions with clinicians during an advisory board, with non-response measured as, "…*if they*

experience more severe exacerbations than the year prior to treatment AND/OR, in case of equal number of severe exacerbation if they experience more moderate exacerbations than the year prior to treatment". Based on these criteria, the response rate for patients at the end of the 52-week trial from the ITT population for dupilumab was 94.2%. Clinical experts to the EAG agreed that these criteria are in line with what they would apply in clinical practice.

In addition to responder status, patients receiving dupilumab may also discontinue treatment at the end of the decision tree. This is based on the rate of discontinuations observed during the trial period (9.3%), which is applied at end of decision tree. The company stated that this is a conservative assumption as some patients may have discontinued during the trial period and yet in the model they receive the costs of 52 weeks of dupilumab.

In addition to COPD severity, patients are also split based on exacerbation status (no exacerbation, moderate exacerbation and severe exacerbation). The company stated that due to exacerbations often being fewer in clinical trials than in a real-world setting, baseline annualised exacerbation rates were based on pooled data from both trial arms from the year prior to trial randomisation, shown below in Table 27. This was applied to patients on background therapy only, with a treatment effect applied to then estimate exacerbation rates in the dupilumab arm (see Section 4.2.3.3 for further details).

Table 27. Baseline annualised rate of exacerbations

COPD severity group	Background Therapy - All Patients	
	Moderate Exacerbation	Severe Exacerbation
Mild	1.8	0.2
Moderate	1.9	0.3
Severe	2.0	0.3
Very Severe	2.0	0.4

Abbreviations: COPD, chronic obstructive pulmonary disease

Moderate and severe exacerbation states were further stratified to capture the number of exacerbations experienced (1, 2 or ≥3). The distribution of patients based on number of exacerbations was based on pre-randomisation trial data (year prior) for all patients in the base-case analysis and was assumed to be the same for both treatment arms. The proportion of patients experiencing each number of exacerbations (0,1,2 or ≥3) was also assumed to be the same across each COPD severity group, shown in Table 28. The EAG notes that the CS incorrectly states that the distribution of patients based on number of exacerbations was based on the trial period and split between responders and non-responders (dupilumab arm), in which non-responders have the same

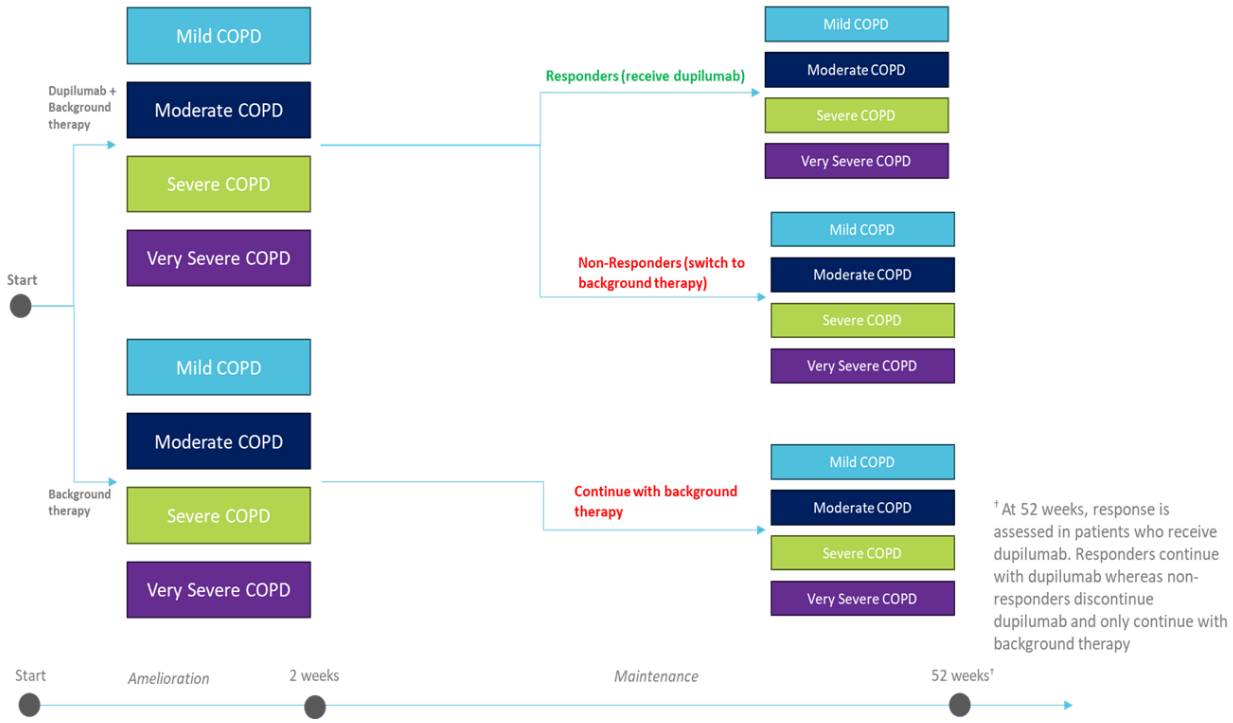
split as the background therapy only arm applied. This was not the case in the company's base-case economic model. However, the company did include data in the model to use direct trial data as a scenario analysis based on the proportion of patients who experienced exacerbations in each treatment arm from the pooled ITT analysis.

Table 28. Distribution of patients having one or more exacerbations used in the company base case analysis

Number of exacerbations	Proportion
Patients having ≥1 moderate:	
1 moderate exacerbation (only)	0.55
2 moderate exacerbations (only)	0.23
3+ moderate exacerbations (only)	0.22
Patients having ≥1 severe:	
1 severe exacerbation (only)	0.84
2 severe exacerbations (only)	0.13
3+ severe exacerbations (only)	0.03

For patients who had ≥3 exacerbations, the average number was estimated from pooled trial data in the ITT population. This estimated that patients having ≥3 moderate exacerbations had an average of 3.84 moderate exacerbations and patients with ≥3 severe exacerbations were estimated to have an average of 3.75 severe exacerbations.

Figure 9. Diagram of decision tree model structure used to represent the trial period, reproduced from Figure 24 of CS



4.2.3.2 Long-term Markov model

Patients enter the Markov state transition model based on the distribution of patients at the end of the 52-week trial period split by both COPD severity (mild, moderate, severe, very severe) and recent exacerbation status (none, ≥1 moderate, ≥1 severe). This results in 12 health states plus an absorbing state for death.

The Markov model uses a lifetime time horizon with an annual cycle length and a half-cycle correction is applied.

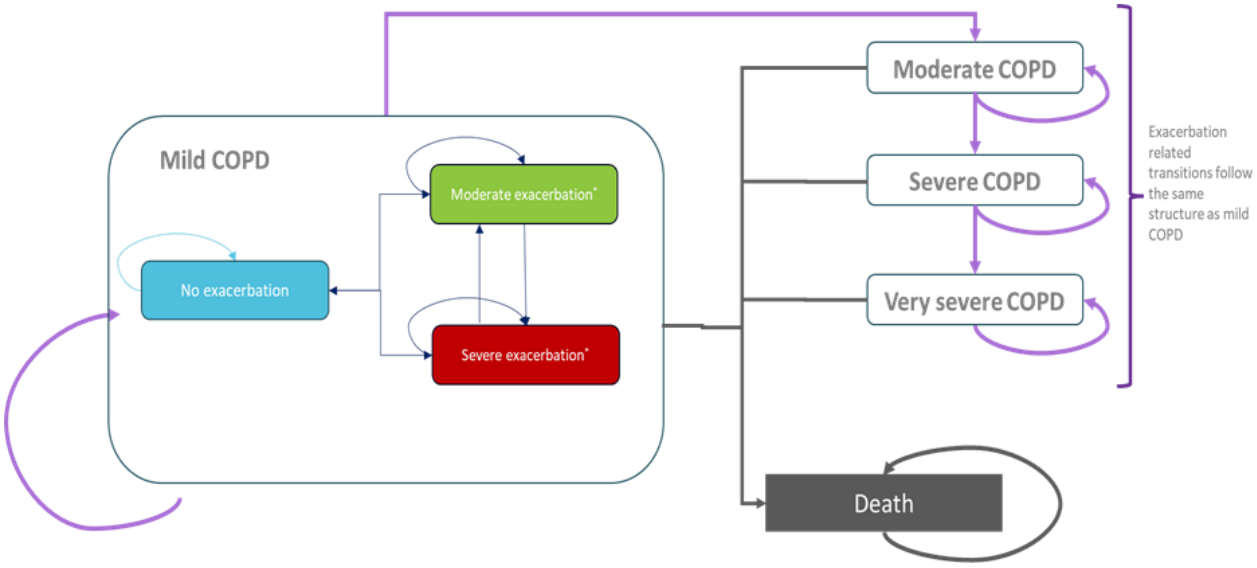
In each model cycle, patients may remain in the same COPD severity health state, transition to a worse COPD severity health state or progress to death. States are also included to represent exacerbations, varying by level of severity (no exacerbations, ≥1 moderate and ≥1 severe), and can be experienced within each COPD severity health state. For example, a patient may remain in the moderate COPD health state within a cycle but go from experiencing no exacerbations in the previous cycle to moderate exacerbations in the current cycle. As with the decision tree, patients

experiencing either moderate or severe exacerbation in a given cycle are further stratified based on the number of exacerbations (1, 2 or ≥3). Therefore, the model includes two separate types of transitions that can occur within the long-term Markov model:

- Within COPD severity health state transitions in which COPD severity remains the same yet patients may experience exacerbations, separated by severity and frequency. Patients may transition between the following states in each cycle:
    - no exacerbation,
    - ≥1 moderate exacerbation;
    - ≥1 severe exacerbation.
- Between COPD severity health state transitions in which patients may progress to a more advanced severity of COPD, based on the GOLD criteria, or death.

The long-term Markov model diagram is shown in Figure 10, replicated from the CS. The data used to inform the two types of transitions within the Markov model are described in further detail in Section 4.2.4.

Figure 10. Diagram of Markov model structure used to estimate the post-trial period, reproduced from Figure 25 of CS



Abbreviations: COPD, chronic obstructive pulmonary disease.

4.2.3.3 EAG critique

Overall, the EAG is satisfied that the model structure captures the main features of COPD through a focus on COPD severity and impact of previous exacerbations (both severity and frequency). However, there are several aspects that the EAG has concerns with.

The EAG notes that a one-year cycle length is not in line with the regularity of dupilumab administration and may not capture the timings of key clinical events. The EAG notes that this is particularly a limitation in the implementation of a treatment-effect maintenance period for dupilumab (see Section 4.2.5) as due to the annual cycle length, scenarios cannot be applied in which it lasts between 0-1 years. During clarification, the EAG asked the company to justify the annual cycle length or adapt to a monthly cycle. The company response stated that the use of the annual cycle length was appropriate to capture the longer impact of exacerbations on quality of life (QoL) and aligning with key model inputs, such as future risk of exacerbations based on the previous year and the efficacy response criteria. The EAG agrees with the stated reasons for an annual cycle length but notes that a limitation of the model is the inability to apply a treatment-effect maintenance period of less than one year.

The EAG agrees that using data directly from the clinical trials may underestimate the exacerbation rate experienced in clinical practice, and notes that clinical experts stated how COVID-19 may have impacted outcomes during the trial period. A systematic review and meta-analysis of the effects of COVID-19 on COPD exacerbations reported that, "*there was a 50% reduction in admissions for COPD exacerbations during the COVID-19 pandemic period compared to pre-pandemic times*".[9] Therefore, the EAG agrees that using data on the baseline rate of exacerbations from the year prior to randomisation in the base-case analysis is appropriate as this allows the modelled population to remain most in line with the trial population. However, the EAG notes that FEV_1 would also be expected to be higher during a trial period, which was confirmed by clinical experts, and considers it inappropriate to assume exacerbations in the trial period are not reflective of a real-world setting and yet patients FEV_1, and therefore changes in COPD severity, is. This is seen through the improvements observed in patients FEV_1 during the trial period in both treatment arms, which clinical experts to the EAG stated is most likely due to optimising treatment, as discussed in Section 3.3.2.1. During clarification, the EAG requested a scenario analysis in which the distribution of patients in each GOLD stage at the start of the Markov model is informed by the distribution at trial baseline (equal to that shown in Table 26) to remove any 'trial effects', with the treatment effect

observed in the trial applied to inform the dupilumab starting distribution. In response to clarification, the company stated that the rationale for using observed FEV_1 was to retain as much trial data in the model as possible, with the focus being exacerbations due to being the primary trial endpoint. The company provided the results of the requested scenario analysis in which the distribution of patients in the dupilumab arm across each GOLD stage at the end of the trial period is informed by the differences in the proportions of patients between the two trial arms. Further detail is provided in Section 4.2.5. Due to the aforementioned reasons, the EAG considers this to be the most appropriate scenario and apply this in the EAG preferred base-case. The EAG notes that this reduced the company's base-case ICER by ≈£700.

The EAG identified some minor errors in the model relating to applying discounting a year too early and applying the start age of the Markov model incorrectly. These were amended during clarification.

4.2.4 Transition probabilities

As noted above, the long-term Markov model includes two separate types of transitions. Data used to inform both types of transition are described in more detail below.

4.2.4.1 Annualised rate of exacerbation - Within COPD severity health state transitions

Transitions *within* each COPD severity health state (no exacerbation, ≥1 moderate exacerbation or ≥ severe exacerbation) are based on exacerbation history in the previous year. Therefore, in the first cycle of the Markov model, this is dictated by the end states of the decision tree. Due to a lack of granular data from the NOTUS and BOREUS trials, future exacerbation probabilities are informed by Whittaker *et al.* 2022.[2] This study reported adjusted incidence rate ratios (IRR) for moderate or severe exacerbations based on prior exacerbation status (1, 2, ≥3 exacerbations [stratified by moderate or severe]) compared to patients who had no exacerbations in the previous year (reference rate), shown in Table 29.

Whittaker *et al.* 2022 is an observational study of patients with COPD who are registered at general practices across the UK, identified through the Clinical Practice Research Datalink (CPRD) Aurum. Linked data to Hospital Episode Statistics (HES) are also used. Within this study, patients are classified as having a moderate exacerbation based on, "*…events recorded in the general practice (CPRD Aurum) using a combination of exacerbation diagnosis codes, antibiotic and oral corticosteroid prescriptions prescribed together for 5–14 days, and recorded symptoms based on a previous*

validated definition of exacerbation in primary care."[2] Severe exacerbation events were defined as, "*…COPD, and lower respiratory tract infection events leading to a hospitalisation as recorded in HES*".[2] Whittaker *et al.* 2022 provided subgroup IRRs based on patients with eosinophils (EOS) ≥300 cells/µL only, which was used by the company as most appropriate to the population of the decision problem.

Table 29. Incidence rate ratio of future moderate/severe exacerbations by baseline exacerbation history (frequency and severity) in patients with blood eosinophils ≥300cells/µl, reproduced from Table E7 of Whittaker *et al.* 2022[2]

Baseline exacerbation history	Adjusted IRR* (95% CI)	
	Moderate exacerbation	Severe exacerbation
None	1 (ref)	1 (ref)
1 moderate only	1.78 (1.70 to 1.86)	1.21 (1.12 to 1.31)
2 moderate only	2.44 (2.32 to 2.58)	1.38 (1.25 to 1.53)
≥3 moderate only	3.94 (3.75 to 4.14)	1.70 (1.56 to 1.84)
1 severe	2.48 (2.29 to 2.68)	2.66 (2.43 to 2.92)
2 severe	2.27 (1.96 to 2.62)	3.86 (3.25 to 4.58)
≥3 severe	2.15 (1.71 to 2.69)	5.35 (4.33 to 6.61)

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; ref, reference

* Adjusted for the following baseline characteristics: age, sex, smoking status, GOLD-defined lung obstruction, mMRC score, comorbidities, BMI group, socioeconomic deprivation, COPD medication use

The incidence rate of moderate and severe exacerbations during follow-up for patients who previously had no exacerbations was not available separately by GOLD COPD severity stage in Whittaker *et al.* 2022.[2] Therefore, the company used data from Wallace *et al*. 2019[25] to adjust the reference rates of exacerbations as they stated that this presented rates of moderate and severe exacerbations split by GOLD severity for patients with no recent prior exacerbations. It was not clear in the CS how data from Wallace *et al.* had been used and the EAG could not identify the data presented in the CS from the study. During clarification the company explained that the reported crude rates of exacerbations per 100 person years, split by COPD severity in Wallace *et al.* 2019 were used to estimate relative rates of exacerbations (compared to mild [GOLD stage 1]). A weighted average relative rate was then calculated which accounted for the distribution of patients who had no previous exacerbations reported in Whittaker *et al*. 2022.[2] This was used to adjust the reference incidence rate of exacerbations from Whittaker *et al.* 2022 (annual rate 0.64 moderate and 0.126 severe) to obtain baseline annual rates based on COPD severity groups (further details provided in response to CQ B16), shown in Table 30.

Table 30. Reference rates of exacerbations by GOLD severity group for patients with no prior exacerbation, reproduced from Table 47 of the CS

GOLD Severity	Reference Rate	
	Moderate Exacerbation	Severe Exacerbation
Mild	0.5	0.1
Moderate	0.61	0.11
Severe	1.02	0.2
Very Severe	0.82	0.34

Abbreviations: GOLD; Global Initiative for Chronic Obstructive Lung Disease

To estimate annual transition probabilities for the background therapy arm only, the company multiplied the reference rate of exacerbations (split by each GOLD severity stage and exacerbation severity) by the corresponding IRR, which was then converted to an annual probability. For example, for patients in the moderate COPD health state with two recent moderate exacerbations (previous cycle), the probability of having one or more moderate exacerbations in the following cycle is calculated as:

1. *Rate: Reference rate (0.61) * IRR (2.44) = 1.4884*
2. *Annual probability of ≥1 moderate exacerbation: 1- exp(-1.4884*1) = 0.774*

As previously discussed, patients who have ≥1 exacerbation are further stratified by number. The distribution of patients by number of exacerbations is the same as that used in the short-term decision tree, previously presented in Table 28.

For patients in the dupilumab arm, a treatment effect is applied in the base-case analysis to the background therapy only transitions, described further in Section 4.2.5.

4.2.4.2 Change in FEV_1 - Between COPD severity health state transitions

Due to the progressive nature of COPD, patients can only progress to a more severe COPD health state or death. As previously discussed in Section 4.2.3, the starting distribution of patients across the four COPD severity health states is dictated by the pooled trial data.

Due to a lack of long-term data beyond the 52-week trial period, annual transition probabilities to more severe COPD states are based on a regression model published in Fenwick *et al.* 2021.[26]

Fenwick *et al*. used a random intercept regression model fit to three-year data on COPD patients from the TORCH study to estimate annual natural decline in FEV_1.[27] The regression model estimated an annual decline of 40.9ml per year for patients without a recent exacerbation and an additional 30.6ml for patients with a recent exacerbation (71.5ml).

As COPD health states in the economic model are classified by $ppFEV_1$, in line with the GOLD criteria, conversions from FEV_1 were required to estimate the time taken for an average patient to move from the midpoint of one COPD severity health state (i.e. 65% $ppFEV_1$ in the moderate health state) to the threshold of the next health state. The approach used to estimate annual transitions between COPD health states is described further below:

1. FEV_1 for an average person with the starting age (65) and height of patients from the pooled BOREAS and NOTUS trials is calculated using the European Respiratory Society (ERS) reference equation from Quanjer *et al*. 1993.[28] This is then calculated for each subsequent year.
2. For patients in the moderate health state, a starting $ppFEV_1$ value of 65% is used to represent a patient being at the midpoint of the moderate COPD severity health state. Based on the FEV_1 of an average person calculated in step 1 and a starting $ppFEV_1$ of 65%, the FEV_1 of the modelled patients was estimated (65% * average person FEV_1).
3. In each subsequent year, a decline in FEV_1 of 40.9ml is applied from Fenwick *et al.* for patients with no recent exacerbation and 71.5ml for patients with a recent exacerbation (40.9 + 30.6) to provide separate estimates of annual FEV_1 for patient with/without exacerbations.
4. FEV_1 in each year is converted to $ppFEV_1$.
5. Time taken in years for patients to reach the threshold of the subsequent COPD severity health state is estimated.
6. Assuming a constant rate, time was converted to an annual probability.
7. This same process was repeated for patients starting at the midpoint of the severe health state (40%) to estimate an annual probability of transition to the 'very severe' health state. Transition probabilities for mild to moderate health states were assumed to be the same as moderate to severe based on a lack of data. However, the EAG notes that this applies to a small proportion of patients in the model who experienced an improvement in FEV_1 during the trial period on dupilumab, causing them to start the long-term Markov model in the mild health state.

As Fenwick *et al*. was not based on COPD patients with Type 2 inflammation, the company state that using the estimates of decline directly may underestimate the rate of decline of patients in the current appraisal, as studies have shown Type 2 inflammation is associated with accelerated lung function decline. Therefore, in the estimation of annual transition probabilities, described above, the company applied a multiplier of 1.52 to the annual FEV_1 decline from the Fenwick *et al.* regression estimates. This was applied for both those without exacerbations and those with recent exacerbations. The 1.52 multiplier was estimated based on COPD subgroup data from the CanCOLD study[29] comparing COPD annual rate of decline based on EOS count, described on page 129 of the CS. This results in an annual decline in FEV_1 of 62.17ml for patients with no exacerbations and 108.68ml for patients with a recent exacerbation. As the Fenwick *et al.* study did not differentiate between severity of exacerbation, the decline calculated for patients with recent exacerbation is applied to all recent exacerbations, regardless of severity.

4.2.4.3 EAG critique

Due to a lack of long-term data from the clinical trials to estimate transitions between exacerbation states, the EAG considers the use of Whittaker *et al.* 2022[2] to be appropriate to inform future exacerbations but notes concerns with the additional adjustments made based on Wallace *et al.* 2019.[25] Adjustments to the reference rates of exacerbations for those with no previous recent exacerbations were made due to the split by GOLD severity stage not being available from Whittaker *et al.* 2022. In the estimation of the IRRs, Whittaker *et al.* controlled for GOLD stage, therefore, making separate adjustments may result in a double counting of the impact of GOLD severity. In addition, Wallace *et al.* was a study based in the USA during 2012–2013 in which the majority of patients were on double therapy as opposed to triple therapy (19% in GOLD stage 3, 16% in GOLD stage 4 on triple therapy). Therefore, the exacerbation rates reported in this study may be unreflective of current practice in the UK. The EAG also notes that only 32 patients in the study were classified as GOLD stage 4. While this may be expected, the small patient numbers add additional uncertainty around the rates obtained. Based on the above reasons, the EAG has included a scenario analysis in which the reference rate of exacerbations for those with no recent exacerbation is taken directly from Whittaker *et al.* and does not differ between GOLD severity stage.

The annual decline in patients FEV_1 used in the model is 62.17ml for patients with no exacerbations and 108.68ml for patients with a recent exacerbation, regardless of exacerbation severity or frequency in previous year. Fenwick *et al*. used data from the three-year TORCH study[27] to estimate

annual FEV_1 decline. The EAG notes that no patients in TORCH were on triple therapy and therefore annual decline may be overestimated compared to patients who would receive triple therapy. This was confirmed by clinical experts to the EAG. Therefore, applying an additional modifier to account for a faster decline in patients with EOS≥300 may overestimate the annual decline (**Key issue 4** in Section 1). The EAG notes that the company also stated that the indirect treatment comparison (ITC) against roflumilast was not robust as both the REACT and RE2SPOND trials had a high proportion of patients on double therapy, which the company did not consider appropriate to compare with those on triple therapy in BOREAS and NOTUS.

One of the EAG's clinical experts stated that the 40.9ml per year for patients experiencing no recent exacerbations and 72.5ml per year for those with exacerbations, estimated from Fenwick *et al.*, is consistent with what they observe in the whole COPD population. It was noted that patients with EOS ≥ 300 have a more rapid decline in FEV_1, with the 62ml per year estimated by the company's analysis seeming reasonable. Although the clinical expert deemed it reasonable that exacerbations would have an additional added effect, it was difficult to provide an estimate of the magnitude for patients with EOS≥ 300 and therefore was unable to comment on the plausibility of the estimate of 109ml per year for patients with recent exacerbations in the previous year. A second clinical expert to the EAG stated that the annual decline used in in the company's model (62ml for no exacerbations and 108.68ml for patients with a recent exacerbation) is higher than they would expect to see in clinical practice.

The EAG also has a number of concerns about the applicability of the multiplier estimated by the company from the CanCOLD study (Tan *et al.* 2021):[29]

- The majority of patients with COPD in the study had mild disease severity, which is associated with a faster FEV_1 decline than patients with more advanced disease, of which this appraisal is focused on. The study authors note how this may explain differences to previous study findings which, "… *failed to demonstrate a significant relationship between blood eosinophil counts and the rate of change in FEV_1 in patients with moderate-to-severe COPD who were treated with various therapies, including ICS, which may have further modified this relationship*".[29]
- Only 68 of the 466 patients included in the analysis were on ICS, which is associated with a reduction in the rate decline in FEV_1 for patients with EOS≥300. As the majority of patients in

the population of the current appraisal are receiving ICS, using the Tan *et al.* study may overestimate the decline in the population of interest.

- Tan *et al*. controlled for exacerbations (at least 2 versus 1 or fewer) in their regression analysis of FEV_1 decline, therefore, applying the multiplier derived by the company to patients with recent exacerbations may not be appropriate.

The EAG highlights that using the company's estimates of 108.68ml annual decline for patients with a recent exacerbation, it takes 4.5 years for patients to transition from the moderate COPD severity health state to severe COPD and 2.5 years for patients to move from severe COPD to very severe. Based on discussions with clinical experts, the EAG consider this may overestimate the rate at which patients transition between states, although it is difficult to predict as it will differ between patients based number and severity of exacerbations. As the majority of patients in the background therapy only arm have exacerbations during each model cycle, the EAG consider this to favour the dupilumab arm. The EAG also considers a decline of 108.68ml each year for patients with any recent exacerbation, regardless of severity or frequency, may be overestimated. Although this figure is applied in both treatment arms, as patients in the dupilumab arm have a reduced rate of exacerbations applied for the lifetime of the model compared to background therapy only, the EAG notes that this will have a preferential impact in favour of the dupilumab arm.

Based on the above issues, the EAG considers it more appropriate to inform transitions between COPD severity based on the annual decline estimated by Fenwick *et al.*, without the additional adjustment of a multiplier for EOS≥300 (**Key issue 4** in Section 1). This was presented in the company's own scenario analyses (see Table 45 in Section 5.2.2) and is applied in the EAG's preferred analysis. For patients experiencing any exacerbations in the previous year, using this approach results in an average time to transition from moderate COPD to severe of 7.5 years and from severe to very severe of 4.5 years.

4.2.5 Treatment effectiveness

4.2.5.1 Annualised rate of exacerbations

As previously noted in Section 4.2.3, the baseline annualised exacerbation rate was based on pooled data from both trial arms from the year prior to trial randomisation. This was applied to patients on background therapy only, with a treatment effect then applied to estimate annual exacerbation rates in the dupilumab arm during the short-term decision tree, reflecting the trial period. The

treatment effect was calculated from trial data for the ITT population in the form of a rate ratio (RR), whereby the annualised rate of exacerbations (split by both COPD severity and exacerbation severity) observed in the dupilumab arm is divided by the rate observed in background therapy only arm. The rate ratios for all dupilumab patients and for those classified as responders only are calculated separately. The annualised rates from the trial and corresponding RRs are shown below in Table 31 and Table 32, respectively.

Table 31. Annualised exacerbation rates by COPD severity from the pooled ITT BOREUS and NOTUS trials, used to estimate the treatment effect

COPD severity	Background therapy only		Dupilumab + background therapy (all patients)		Dupilumab + background therapy (responders only)	
	Moderate exacerbation	Severe exacerbation	Moderate exacerbation	Severe exacerbation	Moderate exacerbation	Severe exacerbation
Mild	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Very severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: COPD, chronic obstructive pulmonary disease.

Table 32. Calculated rate ratios for all dupilumab patients and dupilumab responders only, used to represent treatment effect

COPD severity	Dupilumab + background therapy (all patients)		Dupilumab + background therapy (responders only)	
	Moderate exacerbation	Severe exacerbation	Moderate exacerbation	Severe exacerbation
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]
Very severe	[redacted]	[redacted]	[redacted]	[redacted]

*Assumed to be the same as severe due to no exacerbations for very severe patients observed in the dupilumab arm
Abbreviations: COPD, chronic obstructive pulmonary disease.

For the annualised exacerbation rates during the decision tree in the dupilumab arm, the RRs for *all dupilumab* patients are applied to the pooled rates from both trial arms in the year prior to trial randomisation. For the dupilumab transition probabilities based on exacerbation rates (during the long-term Markov model), the RRs from *responders only* are applied to the calculated rate of

exacerbations for background therapy only patients, described previously in Section 4.2.4.1, before conversion into an annual probability. Transition probabilities for both treatment arms used in the base-case analysis are presented in Tables 48 and 49 of the CS.

The treatment effect on exacerbations is assumed to apply for the patient's lifetime while they remain on dupilumab.

4.2.5.2 Change in FEV_1

The treatment effect of dupilumab on FEV_1 is applied through the short-term decision tree, which captures the changes in the distribution of patients across each COPD severity health state during the 52-week trial period, due to improvements in FEV_1 (and therefore $ppFEV_1$).

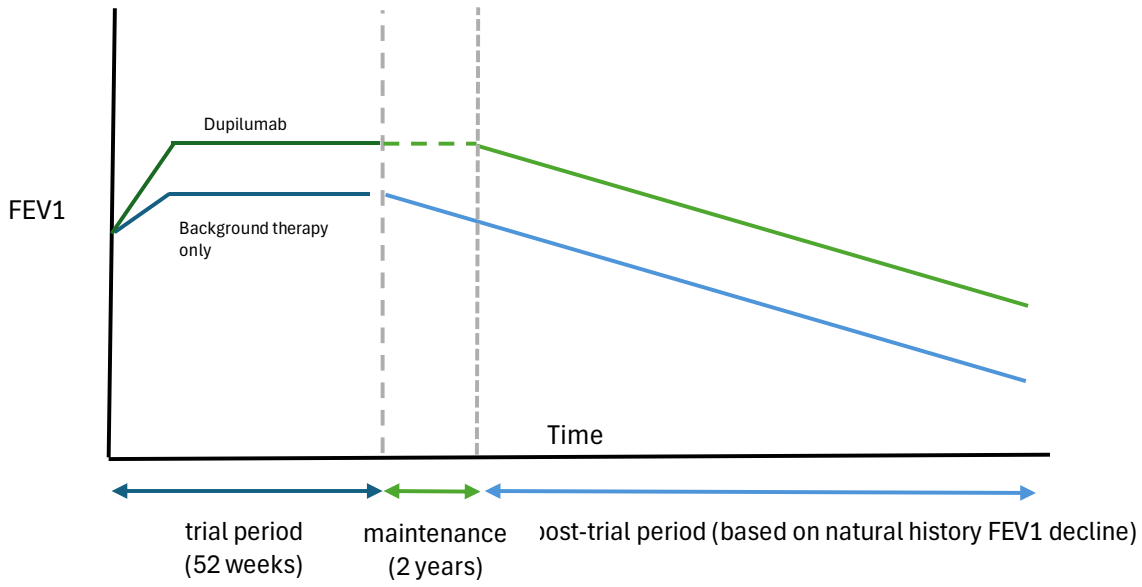
As discussed in Section 4.2.3.3, the EAG requested a scenario to be included in which any 'trial effects' on FEV_1 observed in the 52-week trial period in both treatment arms were removed and the observed treatment effect used to derive the distribution of patients in the dupilumab arm. For patients in the background therapy only arm, the company used the distribution of patients across each COPD severity group observed at baseline. Due to the benefits of dupilumab on FEV_1 being modelled through a change in the distribution of patients in each COPD severity stage, the treatment effect in the requested scenario is applied as an incremental effect on the proportion of patients in each COPD severity stage on background therapy only. For example, the difference in the proportion of patients in the moderate COPD health state at the end of the trial period was -2.4% (44.2% dupilumab arm versus 46.6% background therapy only arm). This 'treatment effect' was then applied to the proportion of patients at baseline in the background therapy only arm (47.9%) to estimate the proportion of patients in the dupilumab moderate health state (45.5%). This same approach was used for both the mild and severe health states. In order to ensure that the proportion of patients in each group summed to 100%, the proportion of patients in the very severe health state was derived using a restrictive approach.

Beyond the 52-week trial period, the economic model applies a treatment effect maintenance period in which there are no transitions across COPD severity health states, i.e. no FEV_1 decline, for a specified time period. The company asserts that data for patients on background therapy only on pre-bronchodilator (pre-BD) FEV_1 by visit suggests that patients FEV_1 began to decline following the end of the 52-week trial period (Figure 26 of CS). Therefore, for patients in the background therapy

only arm, FEV_1 is assumed to decline from the beginning of the Markov model and transition probabilities described in Section 4.2.4.2 are applied.

For the dupilumab arm, the company assumes that the treatment effect on FEV_1 will be maintained for a further two years beyond the end of the trial period (three years in total). Due to a lack of long-term data for dupilumab in COPD patients, the company base-case used long-term data from moderate/severe asthma patients treated with dupilumab in the TRAVERSE study.[30] This showed improvements in pre-BD FEV_1 were maintained from the 52-week trial period and during the 96-week follow-up. Following the treatment maintenance period, the same transition probabilities between COPD health states as background therapy only are applied. Therefore, due to the initial higher starting FEV_1 for patients in dupilumab, a treatment effect is maintained throughout the lifetime of the model, while patients remain on dupilumab, as shown in Figure 11.

Figure 11. Representation of treatment effect for FEV_1 applied in the economic model



The company also conducted a structured expert elicitation to elicit clinical expert opinion on the length of the treatment effect maintenance period. Results suggested the expected time until decline in FEV_1 may begin would be 6.6 months, which the company rounded to one-year due to an annual cycle length. This was applied in a scenario analysis, resulting in an increase in the probabilistic ICER of almost £4500 (£25,793 to £30,251).

4.2.5.3 EAG critique

Annualised rate of exacerbations

Although the EAG consider the use of the RR derived from the trial and applied to pre-randomisation annualised exacerbation rates to be appropriate, the EAG notes that the primary trial outcome was annualised rate of moderate or severe exacerbations (combined). However, the RR is calculated based on the rate of annualised exacerbations observed in each treatment arm, split between both GOLD severity level and exacerbation severity. Table 17 of the efficacy CSR shows that there was no statistically significant difference in severe exacerbations between the two treatment arms in the 52-week trial period ([redacted]), and as noted in Section 3.3.1, 90% of exacerbations experienced were moderate.

Although the EAG is aware that the trial was not powered to detect statistically significant differences in severe and moderate exacerbations separately, it is noted that differences in severe exacerbations are a key driver of the ICER, due to the associated impact on costs, quality of life and mortality (**Key issue 5** in Section 1). As a difference in exacerbations is modelled for a patient's lifetime while they remain on dupilumab, the EAG considers the benefit may be overestimated. During clarification, the EAG requested that a scenario analysis which assumes no difference in severe exacerbation rates between the two treatment arms.

In response to clarification question B12, the company also noted that the studies were not powered to measure differences in the rate of severe exacerbations. Further detail was provided on differences in the time to first severe exacerbation between treatment arms and the adjusted annualised severe exacerbation rate. The company state how these show a statistically significant difference between arms, yet the EAG notes that it was previously stated how the trials were not *a priori* powered to detect a significant difference in severe exacerbations and so the EAG assumes these are *post hoc* assessments. Clinical experts consulted by the company indicated that the mechanism for moderate and severe exacerbations is broadly similar, suggesting that although the absolute number of exacerbations may differ, the rate reduction would be expected to be similar. While the EAG understands the limitations associated with the small number of severe exacerbations observed in the trial setting, the EAG still considers there to be uncertainty in the magnitude of the reduction in severe exacerbations. Although the EAG does not consider it appropriate to assume no difference in severe exacerbations in the EAG base-case, the scenario

analysis highlights the impact on the ICER in assuming no difference between treatment arms (increases to £61,457) and notes the uncertainty surrounding this outcome.

Change in FEV_1

As patients in the dupilumab arm of the trial had treatment removed at the end of the 52-week trial period, no long-term data are available to observe long-term changes in FEV_1. Clinical experts to the EAG noted that it was a reasonable assumption to apply a maintenance period for the treatment effect, but that it was difficult to estimate an exact period of time. Clinical experts stated that although using data from the dupilumab asthma trial may be reasonable, patients with COPD would be older with more comorbidities and therefore may expect to decline more quickly. During clarification, the EAG asked the company to justify the three-year period in light of differences in the patient populations.

In response to clarification, the company conducted a simple exploratory Matching Adjusting Indirect Comparison (MAIC) of a subgroup of patients in the TRAVERSE study matched to patients in the pooled BOREAS and NOTUS data (more details provided in the company response to CQ B17) based on age and pre-BD FEV_1. The company suggests that their analysis shows there is no increased rate of lung function decline for patients with asthma based on equivalent older age and lower pre-BD FEV_1 of COPD patients. The company also describe how the mechanism of action of dupilumab is expected to be the same in asthma patients as it is in COPD patients and maintains the use of the long-term asthma study to inform the treatment effect maintenance period.

While the EAG agrees that the matched characteristics seem reasonable, the company only weighted the baseline age and pre-BD FEV_1 of the TRAVERSE population. As other possible treatment effect modifiers between the two populations have not been adjusted for, for example co-morbidities, uncertainty remains in the similarity between the populations. When performing an unanchored MAIC, all potential prognostic factors and potential treatment effect modifiers need to be adjusted for; no information has been provided to show that this has been done in the analysis provided by the company. An alternative approach would have been to use propensity score matching using individual patient data from the trials. No information was provided for the choice of the MAIC methodology rather than propensity score matching.

While the EAG considers the evidence provided by the company to be reasonable, based on a lack of long-term data in the population of interest, the treatment effect maintenance period is considered

to be highly uncertain in the economic model (**Key issue 6** in Section 1). However, due a lack of alternative data to inform the maintenance period, the EAG agrees with the use of the asthma trial data in their preferred base case, but considers it to be an optimistic assumption. The EAG also requested a scenario analysis during clarification with no maintenance period included; this resulted in a deterministic ICER of £31,488.

4.2.6 Discontinuation

As noted in Section 4.2.3.1, the rate of discontinuations observed during the trial period (9.3%), was applied at end of decision tree. Following an EAG request, the company clarified that discontinuations due to COVID-19 related reasons were also included in the 9.3%. Based on discussion with clinical experts, the company stated that although COVID-19 related infections will have increased discontinuations during the trial period, which may not be expected in current clinical practice, the pandemic also reduced non COVID-19 related infections which may have otherwise resulted in discontinuation. Therefore, the company consider that removing discontinuations due to COVID-19 would not provide a more valid estimate of the true discontinuation rate in the first year of treatment. Removing these patients results in a rate of 8.5% and a minimal reduction in the corresponding ICER.

As no long-term data on discontinuation rates were available beyond the initial 52-week trial period, the company used Sanofi homecare data from asthma patients treated with dupilumab. Data was available for three years and suggests an annual discontinuation rate of approximately [redacted]%. Clinical experts from the company's advisory board meeting suggested an annual rate of between 15–20% for patients on biologics. Therefore, as this was in line with the rate observed in asthma patients, the company applied 15% in the base-case analysis.

Two additional scenario analyses were also conducted using alternative sources; 25.8% per year based on a company-sponsored structured expert elicitation and 22.4% based on a study of severe asthma patients treated with biologics (Mansur *et al.* 2022).[31] The two scenario analyses reduced the deterministic ICER by approximately £3,500 and £2,500, respectively.

Following discontinuation of dupilumab, patients are assumed to receive background therapy only and the associated outcomes (exacerbation rates, costs and utilities). Patients classed as non-responders and patients who discontinue are assumed to lose the treatment effect on FEV_1 from the

start of the Markov model, in line with background therapy only patients; i.e. for discontinuers and non-responders there is no treatment-effect maintenance period and patients have the COPD severity health state transitions probabilities associated with background therapy only applied. During clarification, the company noted that this was implemented in the model incorrectly in the original base-case and amended in the updated base-case model.

During clarification, the EAG requested that the company used Kaplan-Meier (KM) data on the patients who discontinued during the pooled clinical trials and fit parametric curves to extrapolate the data to estimate the long-term discontinuation of patients. The company provided the KM curve with parametric curves fit using the Weibull, log-normal, log-logistic and Gamma distributions. From the provided goodness-of-fit statistics, the log-normal was deemed to be the best fitting curve, however, the company stated that the predictions are at odds with clinical opinion and real-world evidence on dupilumab usage in the UK (asthma patients). The company did not include the extrapolated curves as an option in the economic model in order to observe the impact on the ICER. Due to time constraints, the EAG was unable to perform this with the data available. However, clinical experts to the EAG noted that assuming the same discontinuation rate of dupilumab in asthma patients is a reasonable assumption. Due to the uncertainty of this input due to a lack of long-term data, the EAG has also conducted an additional scenario in which the discontinuation rate is equivalent to that observed during the trial period (see Section 6.2).

4.2.7 Mortality

The economic model uses UK national life tables from 2020–2022 to represent general population mortality associated with age.[32] The proportion of COPD-related deaths (ICD-10 codes J40-J44) in the general population were removed from the UK national life tables in order to remove any potential confounding.

Excess mortality associated with each COPD severity stage (measured using airflow limitation GOLD stages 1–4) was sourced from Whittaker 2024.[1] This study estimated all-cause mortality hazard ratios (HRs) associated with COPD severity produced using a Cox proportional hazards model, which adjusted for numerous patient baseline characteristics, co-morbidities and exacerbation history in

the year prior to index date. As mild COPD was used as the reference group in Whittaker *et al.* 2024, this group was assumed to have the same mortality as the general population.

In addition, the company states that the review of previous economic models showed that COPD mortality is associated with both COPD stage and exacerbations. Therefore, to account for an increased risk of mortality due to exacerbations, a separate case fatality rate (CFR) is applied per severe exacerbation. This is based on a previous meta-analysis by Hoogendoorm *et al.* 2011[33] that included six studies to estimate a CFR of 15.6% associated with severe exacerbations. The company states that as the impact on mortality of moderate exacerbations is not included, this is a conservative estimate.

The company also includes an option in the economic model in which excess mortality related to exacerbations is taken from Whittaker 2022[2] (the same source used for informing exacerbation rates based on previous exacerbations, as described in Section 4.2.4.1). This study uses the same data source of UK patients that is used in Whittaker *et al.* 2024 in the company's base case for COPD severity mortality. This applies a mortality incidence rate ratio (IRR) based on baseline frequency and severity of exacerbations (whereby no recent exacerbations is used as the reference). The EAG notes that using this option for excess mortality related to exacerbations instead of the CFR for severe exacerbations (15.6%) increases the ICER (deterministic) from £25,515 to £36,449. The EAG notes a preference for using consistent data sources in the economic model when appropriate.

4.2.7.1 EAG critique

While the EAG has observed evidence of an impact on mortality of both COPD severity and exacerbations, there is concern that applying the separate CFR may double count the impact of exacerbations on mortality that may already have been accounted for within the COPD severity excess mortality (**Key issue 7** in Section 1). As previously noted, Whittaker *et al*. 2024 controlled for exacerbation history in the regression models used to estimate the hazard ratio associated with COPD severity. This was confirmed to the EAG by the study author (Whittaker, personal communication, 6th December 2024). The author stated that the analysis for all-cause mortality and GOLD ppFEV$_1$ were adjusted for baseline exacerbations defined as "none" or "any".

In addition to HRs for all-cause mortality associated with COPD severity (airflow limitation), Whittaker *et al*. 2024 also performed separate analyses to estimate HRs associated with both exacerbation severity and frequency on mortality. It was stated in Whittaker *et al. that, "…Although*

increasing frequency and severity of exacerbations were associated with all-cause and COPD-related mortality, the association was lower in magnitude compared with airflow limitation and poorer functional limitation (GOLD groups B and D), potentially reflecting those effective therapies exist to prevent exacerbations in those with a history of frequent or severe events".[1] The study also found that for patients with poorer lung function, measured by ppFEV$_1$, a greater proportion of patients are more likely to die within 30 days of an exacerbation. The EAG considers that the increased risk of death due to exacerbations may therefore already be captured in the risk of death related to COPD severity.

Hoogendoorm *et al.* 2011[33] reports a meta-analysis of six studies. The EAG notes that none of the studies included in this meta-analysis were UK based, and all studies may now be considered relatively out of date (the most recent study included used data collected between 2000–2005 in Norway). During clarification, the EAG asked if any literature searches had been conducted to identify more recent studies. The company noted the use of the alternative source of Whittaker *et al.* 2022 used in the model, previously discussed by the EAG and notes that the 2014 UK National COPD Audit Report, provides a severe exacerbation case fatality rate ranging from 2.1% to 17.8%. The most recent report from the National Asthma and Chronic Obstructive Pulmonary Disease Audit Programme (NACAP), October 2018–March 2020, reported that 6.1% of COPD patients died within 30 days of a hospital admission and 11.9% within 90 days.[34]

While clinical experts to the EAG noted that they expect an additional risk of mortality associated with severe exacerbations, they were unsure if 15.6% was appropriate, with one clinician noting that this seemed higher than expected.

During clarification, the company acknowledged that the standardised mortality ratios (SMRs) from Whittaker *et al.* 2024 may include exacerbation risk and provided a range of new scenarios to try to address the uncertainty associated with applying an additional CFR (response to CQ B22). The company argues that removing the CFR for severe exacerbations is problematic due to the following reasons:

- The SMRs calculated by Whittaker *et al.* are based on standard care treatment consisting of dual and triple therapy only and therefore the SMRs are not fully applicable to the dupilumab treatment arm, which would be expected to reduce mortality through reduced exacerbation rates.

- Removing a CFR removes any benefit due to the decrease in moderate and severe exacerbations due to dupilumab.
- Two-thirds of patients in Whittaker *et al.* had no prior exacerbations and therefore risk of mortality may be lower in this population.

The EAG notes that the CFR applied by the company in their base-case analysis is also based on treatment without dupilumab, and as previously mentioned, may not be representative of current UK practice. The EAG disagrees that removing the CFR removes any benefit due to decreased exacerbations as patients in the dupilumab arm will still have reduced costs associated with fewer exacerbations and less disutilities applied compared to background therapy only. The EAG acknowledges the limitation that the majority of patients in Whittaker *et al.* 2024 had not had a prior exacerbation in the previous year and therefore may not be fully representative of the current population of interest. However, a more appropriate alternative was not provided.

The company suggested that a plausible alternative to their base-case assumption would be to remove the CFR and apply separate SMRs for each COPD severity health state by treatment arm. The company state that this would account for the benefit of dupilumab on mortality that cannot be captured through using only the Whittaker *et al* 2024 SMRs.[1] As the BOREUS and NOTUS trials were not powered to detect differences in mortality, the company assumed that the improvement in mortality due to the introduction of dupilumab would be equal to the reduction in mortality observed between dual (LABA/LAMA) versus triple (LABA/LAMA/ICS) therapies (HR 0.72, 95% confidence interval 0.53 to 0.99, p = 0.042) from the IMPACT clinical trial.[35] Therefore, the company applied the reported SMRs for background therapy only patients, whereas for the dupilumab arm, each SMR was multiplied by 0.72, shown in Table 33. As the model was not structured to apply separate SMRs by treatment arm, this scenario was implemented manually by the company by running the model twice and manually calculating the corresponding ICER (£23,210).

The EAG notes, however, that the approach used by the company to implement this scenario results in patients who discontinue dupilumab or who are non-responders also receiving the adjusted SMRs and therefore incorrectly receiving a mortality benefit. The EAG implemented the scenario directly in the company's model and the resulting ICER was £35,607 (see Section 6.3).

Table 33. SMRs applied in the company's scenario analysis, adjusted based on IMPACT study

COPD severity	Unadjusted SMRs (background therapy only arm)	Adjusted SMRs (dupilumab + background therapy arm)
Mild COPD	1.000	1.000
Moderate COPD	1.450	1.044
Severe COPD	2.330	1.678
Very Severe COPD	4.100	2.952

Abbreviations: COPD, chronic obstructive pulmonary disease; SMR, standardised mortality ratio

While the EAG notes that this approach removes the issue of double counting, the extent to which dupilumab may reduce mortality is uncertain as the study was not powered to detect this. However, despite the large number of exacerbations observed across the pooled trials in the one-year treatment period, there was no difference in mortality between treatment arms (1.5% of placebo patients versus 1.6% of dupilumab plus background therapy patients). In addition, the applicability of the IMPACT data to adjust the SMRs is also uncertain. A recent editorial letter highlighted how the IMPACT trial (including others) was not powered to examine the influence of triple therapy on mortality and mortality benefits observed for triple therapy may be attributed to the higher mortality rates from abrupt discontinuation of ICS for patients in the LABA/LAMA arms.[36] The EAG, therefore, does not consider there to be robust evidence of a mortality benefit of dupilumab that can justify the use of treatment arm specific SMRs.

The EAG notes that the inclusion of an additional excess mortality for severe exacerbations is a key driver of the ICER. This is shown in the EAG requested scenario in which no excess mortality beyond that associated with COPD severity was included, with a resulting ICER of £49,954 (deterministic). Considering that the clinical trials showed no statistically significant difference in severe exacerbations between the two treatments, the EAG considers this to be a key uncertainty in the model (**Key issue 7** in Section 1). In the EAG base-case, the EAG preferred not to apply a separate mortality impact of severe exacerbations as the EAG considers this will double count the impact already controlled for in the Whittaker *et al.* 2024 hazard ratios.[1] However, it is acknowledged that this may underestimate the impact of severe exacerbations on mortality. An additional scenario analysis on the EAG's base-case is also included which uses the excess mortality for exacerbations

from Whittaker *et al.* 2022 due to the EAG's preference to use a consistent data source with other inputs used in the model.

4.2.8 Cardiovascular events

Based on the increased risk of cardiovascular (CV) events associated with COPD, particularly due to exacerbations, the company includes disutilities and costs (see Sections 4.2.9 and 4.2.10) to a fixed proportion of patients in each exacerbation health state associated with non-fatal CV events.

In the short-term decision tree, the company applied the observed incidence rates from the pooled ITT trials. During clarification, the EAG noted that the proportions used by the company included fatal adverse CV events and that there was not a statistically significant difference between trial arms and therefore asked the company to remove this from the model. The company updated the CV events observed during the trial period to include only non-fatal events (0.53% for the dupilumab + background therapy and 1.28% for the background therapy alone).

Beyond the trial period, non-fatal CV event incidence rates were informed using data from the large international SUMMIT RCT (Kunisaki *et al.* 2018), in lieu of appropriate UK data.[37] It was unclear to the EAG how the company had adjusted the data from Kunisaki *et al.* 2018 to obtain non-fatal incidence rates associated with exacerbation type (none, moderate, severe). Following additional clarification questions, the company provided further details of the methods used (see 'Post clarification follow-up questions'). The company used data on 'all exacerbations' from Kunisaki *et al.* to represent moderate exacerbations, whereas exacerbations requiring hospitalisations represented severe exacerbations. The EAG considers that using 'all exacerbations' for moderate exacerbations will involve double counting as this outcome will include those requiring hospitalisation.

In addition, the EAG identified a recent UK-based study which provides data on non-fatal CV events following exacerbations. During an additional clarification question, the EAG requested that the company used this data source to inform non-fatal CV events in the model. The company stated that due to time constraints and the small impact of CV events on the ICER they were unable to implement this request.

While the EAG has some concerns with the data used for CV events, it is noted that the exclusion of CV events has a minimal impact on the ICER (increase of £123) and therefore no further analysis was undertaken.

4.2.9 Health-related quality of life

4.2.9.1 Health state utility values

Health state utility values used in the company's economic model were informed by health-related quality of life (HRQoL) data collected in the BOREAS and NOTUS trials. In both trials, the St. George's Respiratory Questionnaire (SGRQ) was collected at baseline followed by weeks 4, 12, 24, 36 and 52. EQ-5D-5L was collected in both trials at baseline, and at week 24 and 52 in the NOTUS trial only.

The NICE Reference Case[38] recommends the use of the EQ-5D-3L for the measurement of utility data. Due to the low collection timepoints of the EQ-5D-5L in the NOTUS and BOREAS trials, the company produced a mapping algorithm which utilised data from visits where both the SGRQ (from the pooled trials) and EQ-5D-5L were collected in order to obtain EQ-5D health state utility values. EQ-5D-5L data were cross-walked to EQ-5D-3L using Hernández Alava *et al.* 2017,[39] as recommended by the NICE methods guide.

The company stated that the three identified published mapping algorithms from SGRQ to EQ-5D did not provide a good fit to the EQ-5D data collected in BOREAS and therefore they developed their own algorithm. The company tested both a generalized linear model (GLM) and two-part regression model. After assessment of model performance, the company selected the GLM as the best fitting model, with the predicted mean EQ-5D-3L (following crosswalk) being 0.7158 compared to the observed mean of 0.7125 (further details available on page 135 of the CS and Appendix Q).

Based on the company's mapping exercise, treatment-specific utility values were derived for each COPD severity health state, shown below in Table 34. Utility values were adjusted for age using the Health Survey for England (HSE) 2014 dataset, as recommended by the NICE DSU (Hernández Alava *et al.* 2022.[23]

During clarification, the company noted that treatment specific utility values had been incorrectly applied in the model, which was rectified by the company.

Table 34. Health state utility values used in the company's base-case, derived from mapping exercise of SGRQ to EQ-5D-3L

Health state	Dupilumab + Background Therapy (SE)	Background Therapy Only (SE)
Mild COPD	[redacted]	[redacted]
Moderate COPD	[redacted]	[redacted]
Severe COPD	[redacted]	[redacted]
Very severe COPD	[redacted]	[redacted]

Abbreviations: COPD, chronic obstructive pulmonary disease; SE, standard error.

The company also included a range of alternative utility values sourced from either the literature (Borg *et al.* 2004;[20] Rutten Van Molken *et al.* 2006,[19] Spencer *et al*. 2005[21] and Sadatsafavi *et al.* 2019)[40] or using data EQ-5D-5L data from the NOTUS trial cross-walked to EQ-5D-3L. The EAG notes that the utility values using the NOTUS EQ-5D data are also treatment-arm specific, as with the mapped values used in the base-case analysis.

The EAG notes that Rutten Van Molken *et al.* 2006 was used as the preferred utility source in the appraisal for roflumilast (TA461).[8]

4.2.9.2 Exacerbation disutility

Disutilities associated with both moderate (-0.0204) and severe exacerbations (-0.0649) are included in the economic model, derived from the mapping exercise used for health state utility values in the company's base case. Exacerbation disutility is assumed to last for three months, regardless of severity. The company also includes a scenario analysis using the exacerbation disutilities derived from the NOTUS EQ-5D-5L (mapped to 3L) trial data. The disutility for severe exacerbations from the NOTUS regression analysis was not statistically significant. However, the EAG notes that this is likely driven by the small number of severe exacerbations that occurred during the trial period.

If literature values are used in the model instead of mapped SGRQ data, values for exacerbation disutility were sourced from Rutten Van Molken *et al.* 2009,[41] as used in the NICE guidelines for COPD (NG115).[7] This study estimated disutilities of -0.01 for moderate exacerbation and -0.04 for severe exacerbation, assumed to apply for one year to capture the chronic impact.

4.2.9.3 Cardiovascular and adverse events

As noted in Section 3.3.4, adverse events (AEs) that occurred more frequently in the clinical trials in the dupilumab arm were headache, back pain, urinary tract infection and gastritis. As these AEs were mild and infrequent, the company did not apply an associated disutility. Based on the low difference in frequency between the two trial arms, the EAG consider this approach to be reasonable and notes that inclusion of a disutility would have a minor impact on the ICER.

As discussed in Section 4.2.8, there is a risk of CV events associated with exacerbations applied in the economic model. Disutilities associated with each type of non-fatal CV event were said to be sourced from Sterne *et al*. 2017,[42] shown below with the corresponding duration in Table 35.

Table 35. Disutility associated with CV events, sourced from Sterne *et al.* 2017

CV event	Disutility	Duration
Myocardial infarction	0.096	3 months
Stroke	0.59	3 months
Transient ischemic attack	0.131	1 month
Unstable angina	0.131*	1 month

* Assumed to be the same as a transient ischemic attack
Abbreviations: CV; cardiovascular.

4.2.9.4 EAG critique

The EAG notes that the linear regression for utilities showed that only SGRQ at baseline, severity of airflow obstruction, and exacerbation risk were statistically significant (Table 54 of CS). The coefficient for treatment group and the interaction terms between treatment and severity of airflow obstruction groups were not statistically significant (p-values ranging from 0.22 to 0.79). Therefore, the EAG does not consider there to be evidence of a separate treatment related benefit to justify using treatment arm specific utilities. The EAG also considers this to be applicable for the utility values derived from the NOTUS EQ-5D collected data, as Table 3 of Appendix R shows that there was no statistically significant difference in EQ-5D-5L change from baseline scores in NOTUS between placebo and dupilumab arms. Therefore, it is unclear why the company used treatment specific utilities (**Key issue 8** in Section 1).

During clarification, the EAG requested a scenario in which the utility regression model was rerun to include only statistically significant covariates (i.e. removal of the treatment interaction term and

treatment arm covariates). The resulting health state utility estimates are shown below in Table 36. The disutilities associated with moderate and severe exacerbations derived from the updated analysis were [redacted] and [redacted], respectively. This scenario resulted in a deterministic ICER of £27,237.

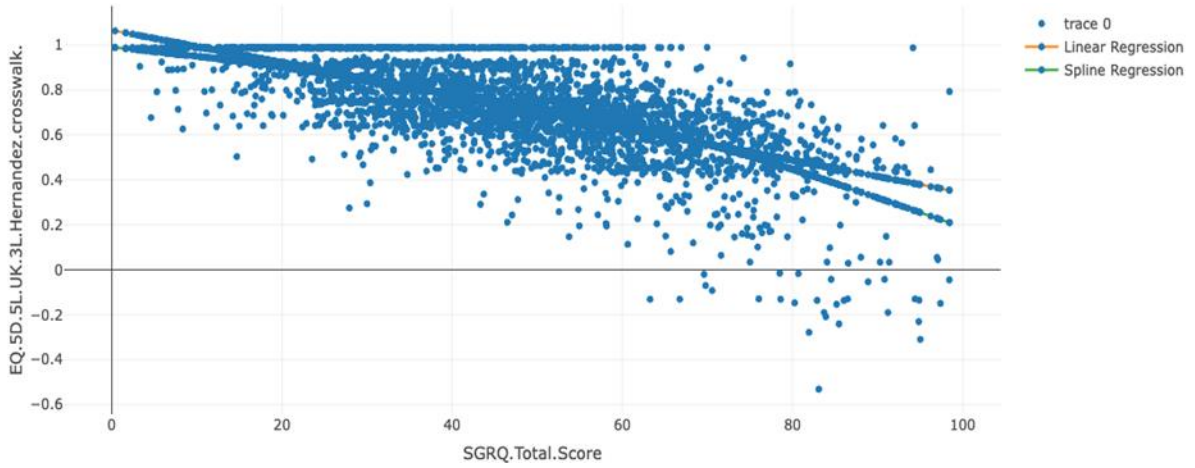
Table 36. Health state utility values derived from company mapping of SGRQ to EQ-5D-3L (cross-walked) using statistically significant variables only

Health state	Utility value (SE)
Mild COPD	[redacted]
Moderate COPD	[redacted]
Severe COPD	[redacted]
Very severe COPD	[redacted]

Abbreviations: COPD, chronic obstructive pulmonary disease; SE, standard error.

Figure 12 displays the scatterplot of EQ-5D-5L responses from the pooled ITT trials (mapped to EQ-5D-3L) and SGRQ total score. The EAG had concerns with the strength of the correlation between the two measures, given that a substantial number of patients with SGRQ scores between 0 and approximately 70 also provided EQ-5D scores of 1 (e.g. perfect health).

Figure 12. Scatterplot of EQ-5D-5L responses from the pooled ITT trials (mapped to EQ-5D-3L) and SGRQ total score. Reproduced from Figure 27 of CS



During clarification the EAG requested further validity and evidence on the correlation between the two measures. The company did not comment on the validity and strength of the correlation in their reply but provided the correlation coefficient for all patients and for those who had a SGRQ total score between 0–70. The Pearson correlation coefficient of -0.65 for the full population suggests a moderate negative correlation between the EQ-5D scores and SGRQ.

The EAG notes that in TA461, both the EAG and committee preference was the use of health state utility values from Rutten van Molten *et al*. 2006.[19] The preference for disutilities was sourced from Hoogendoorn *et al.* 2011[43] as the EAG highlighted that Rutten van Molten *et al.* 2009 used valuations using vignettes, sourced from the Dutch general public.[41] Therefore, the EAG has included results of a scenario analysis using these sources for health state utility values and disutilties. The EAG notes that they also identified a recent study using data from the ETHOS study (Jackson *et al.* 2024)[44] used to estimate the disutility associated with exacerbations in moderate to very severe COPD patients. This study provided disutilities separated by recent exacerbation (-0.055 moderate and -0.08 severe) and the additional ongoing disutility associated with previous exacerbations (-0.014 moderate and 0.025 severe). While the EAG considers this to be a useful and relevant study, values were only available using EQ-5D-5L. In order to maintain the use of EQ-5D-3L throughout, the EAG did not incorporate this study. However, the EAG notes that when applying the disutilities from Jackson *et al.* 2024 associated with recent exacerbations for one month and disutilties reported to represent the persistent effect for 11 months, this did not have a large impact on the ICER.

The EAG was unable to validate the values used in the company's base case analysis for CV event disutilities directly as Sterne *et al.* had sourced values from a previous study. During clarification, the EAG requested further details of the original source or for a scenario analysis using CV disutility values from Ara and Brazier 2010 to be included.[3] Details of the original source were not provided, and the company provided a scenario using values from Ara and Brazier 2010, shown below. Due to not being able to validate the values used in the base-case analysis, the EAG prefer to use values from Ara and Brazier in their preferred assumptions. This reduced the company's ICER by nearly £300.

In light of a lack of evidence for treatment-specific utilities, the EAG prefers the use of the mapped values that are treatment independent in the EAG's preferred base-case. The EAG notes that the ICER did not change substantially when using the company's alternative utility values sourced from the literature (from £24,642 to £26,784). The EAG preferred values are shown below in Table 37.

Table 37. EAG preferred utility values

Event	Utility value	Source
Health state utilities		
Mild COPD	[redacted]	Company mapping of SGRQ from pooled BOREAS and NOTUS trials to EQ-5D-3L, analysis excluding non-significant covariates.
Moderate COPD	[redacted]	
Severe COPD	[redacted]	
Very severe COPD	[redacted]	
Exacerbation disutility		
Moderate	[redacted]	Company mapping of SGRQ from pooled BOREAS and NOTUS trials to EQ-5D-3L, analysis excluding non-significant covariates.
Severe	[redacted]	
CV event disutility		
Myocardial Infarction	0.151	Ara and Brazier 2010; Assuming a perfect health utility of 0.872 and a heart attack <12 months (assumed to be MI) of 0.721
Stroke	0.246	Ara and Brazier 2010; Assuming a perfect health utility of 0.872 and a stroke <12 months (assumed to be MI) of 0.626
Unstable Angina	0.257	Ara and Brazier 2010; Assuming a perfect health utility of 0.872 and an angina event <12 months (assumed to be unstable angina) of 0.615
Transient Ischaemic Attack	0.246	Assumed equal to stroke

Abbreviations: COPD, chronic obstructive pulmonary disease; CV, cardiovascular; EQ-5D-3L, European Quality of Life 5 Dimensions 3 Level Version; SGRQ, St. George's Respiratory Questionnaire.

4.2.10 Resource use and costs

The company's model includes costs related to treatment acquisition, health state costs (COPD management based on severity and exacerbations, CV events and adverse events associated with treatment). These are detailed further in the following subsections. Costs used in the model represent 2022/23 prices, with costs inflated using the PSSRU HCHS pay and prices index when required.[45] Drug costs have been sourced from the British National Formulary (BNF).[46]

4.2.10.1 *Treatment acquisition and administration*

The list price for dupilumab 300mg is £1,264.89 per pack of two pre-filled injection syringes/pens. A confidential patient access scheme (PAS) discount of [redacted] is in place for dupilumab and all results presented in this report include the corresponding PAS. The per cycle (annual) acquisition costs of dupilumab were calculated based on the number of administrations required per cycle.

Background therapy, which is applied in both treatment arms, is assumed to comprise of triple therapy inhalers only, costed using a weighted average basket approach based on the market shares previously described in Section 4.2.2. However, as all triple therapies included have the same cost per cycle, the market share does not impact on the weighted average cost.

Individual treatment costs of dupilumab and background therapies and the associated cost per treatment regime are shown below in Table 38.

Table 38. Dosing schedule/acquisition costs for individual treatments included in the economic model and overall per cycle cost based on treatment arm

Treatment	Dose per administration	Frequency of dose	Administrations per model cycle	Pack size (number of doses)	List price per pack	Per cycle cost	
						List price	PAS price
Individual treatments							
Dupilumab	300mg	Every 2 weeks	26	2	£1,264.89	£16,500.04	[redacted]
Trelegy Ellipta	1 inhalation	Once p/d	365.25	30	£44.50	£541.79	N/A
Trimbow NEXThaler	2 inhalations	Twice p/d	1461	120	£44.50	£541.79	N/A
Trimbow	2 inhalations	Twice p/d	1461	120	£44.50	£541.79	N/A
Trixeo aerosphere	2 inhalations	Twice p/d	1461	120	£44.50	£541.79	N/A
Modelled treatments							
Dupilumab + background therapy						**£17,041.83**	[redacted]
Background therapy only						**£541.79**	**N/A**

Abbreviations: mg, milligrams; N/A, not applicable; p/d, per day; PAS, patient access scheme

The company's base-case assumes that 100% of patients will self-administer dupilumab following a one-off training session. This is costed as one hour of a band 5 hospital nurse time, sourced from the Personal Social Services Research Unit (PSSRU),[45] resulting in a one-off cost of £48 for all patients receiving dupilumab.

4.2.10.2 Health state costs

COPD severity management

Resource use associated with annual management of COPD, based on severity, is sourced from the economic model report produced for the NICE guideline for "Chronic obstructive disease in over 16s: diagnosis and management" (NG115).[7] During NG115, as empirical data could not be sourced for a number of resource use inputs, these were derived from NICE committee consensus. The annual resource use used by the company from NG115 is shown below in Table 39, alongside the original source reported in NG115.

The EAG notes the NG115 also reported the resource use of mucolytics, theophylline and short-acting bronchodilators as part of annual maintenance; however, these were not included by the company as they stated in their clarification response that as these would be experienced in both treatment arms they would cancel each other out.

Table 39. COPD severity health state resource use

Resources	Annual frequency by health state*				Source
	Mild COPD	Moderate COPD	Severe COPD	Very Severe COPD	
GP visit	1	1	1.5	2	NG115 committee consensus
Respiratory team visit	0	0	2	4	NG115 committee consensus
Outpatient visit	0	0	1	2	NG115 committee consensus
Spirometry	1	1	2	3	NG115 committee consensus
Pulmonary rehabilitation	0.02	0.03	0.06	0.09	Price *et al.* 2013

Oral corticosteroids	0.88	0.96	1.7	2.7	Price *et al.* 2013
Home oxygen therapy (proportion of patients)	0	0	0.05	0.4	Price *et al.* 2013
Influenza vaccine (proportion of patients)	0.73	0.73	0.73	0.73	Price *et al.* 2013
CT scan	0	0	0.05	0.1	NG115 committee consensus

*Frequency unless otherwise stated

Abbreviations: COPD, Chronic obstructive pulmonary disease; CT, computed tomography; NG, National Institute of Health and Care Excellence guideline

The unit costs for each corresponding resource use are shown in Table 64 of the CS. Table 40 below presents the total annual health state costs for COPD management applied in the economic model.

Table 40. COPD severity health state management costs, per annual cycle

COPD severity health state	Annual cost
Mild	£100.44
Moderate	£102.86
Severe	£809.94
Very severe	£1,523.26

Abbreviations: COPD, Chronic obstructive pulmonary disease

Exacerbations management

The economic report for NG115 also reported resource use estimates for the management of exacerbations, both requiring hospitalisation and not requiring hospitalisation.[7] The company used the reported resource use for exacerbations not requiring hospitalisation to represent moderate exacerbation management, with amendments made to GP visit resource use based on clinical expert feedback, shown in Table 65 of the CS.

For severe exacerbations, the company noted that clinical experts consulted during an advisory board stated that previous estimates, such as NG115, underestimate the resource use associated with severe exacerbations.[7] Therefore, the company undertook an analysis of Hospital Episode Statistics (HES) usage data during April 2018 to February 2024 in order to estimate resource use

associated with severe exacerbations. This analysis estimated that a severe exacerbation was associated with an average length of stay in hospital of 2.9 days and 14% of patients experienced a readmission to hospital within 30 days of being discharged. Estimated resource use per severe exacerbation and unit costs applied are shown in Table 66 of the CS.

Total costs per exacerbation applied in the company's model are shown below in Table 41.

Table 41. Cost per exacerbation used in company base-case

Exacerbation type	Total cost
Moderate	£105.04
Severe	£4,261.60

4.2.10.3 Cardiovascular and adverse events

The company include the costs of managing non-fatal CV acute events included in the economic model, as described in Section 4.2.8. Unit costs for the management of each CV event were sourced from NHS Reference Costs 2022/23[47] and a weighted average annual cost was produced based on the proportion of patients assumed to experience each type of CV event, as shown in Table 42.

The EAG was unable to replicate the exact unit costs used in the company's model derived from NHS Reference Costs. However, using alternative values that the EAG considered appropriate had an almost negligible impact on the ICER (£1) and therefore no changes have been made to the model.

Table 42. Cardiovascular event management costs

CV event	Proportion of CV events	Unit cost	Source
Myocardial infarction	41.5%	£2,074.28	NHS Reference Costs 2022/23. EB10A-E, Actual or Suspected Myocardial Infarction
Unstable angina	30.5%	£3,531.61	NHS Reference Costs 2022/23. AA22C-G, Cerebrovascular Accident, Nervous System Infections or Encephalopathy
Stroke	19.9%	£1,055.79	NHS Reference Costs 2022/23. EB13A-D, Angina

Transient ischemic attack	8.2%	£1,333.18	NHS Reference Costs 2022/23. AA29C-F, Transient Ischaemic Attack
Weighted average cost of CV events applied in the model	**£2,254.97**		
Abbreviations: CV, cardiovascular.			

For the adverse events included in the model (noted in Section 3.3.4), a one-off cost of a GP visit (£49 sourced from PSSRU) is applied to the reported proportion of patients experiencing each event in each treatment arm.

4.2.10.4 EAG critique

Clinical experts to the EAG noted that it is unlikely that 100% of patients will be able to self-administer dupilumab, due to age, frailty or other complicating factors, and noted that it would be reasonable to assume 5% of patients require assistance. During clarification, the company provided a scenario analysis in which 5% of patients received support with administration via a hospital outpatient appointment (resulting in an ICER of £26,680). The EAG considers it appropriate to include a proportion of patients requiring administration assistance in the base-case analysis. In the EAG preferred base-case it is assumed that 5% of patients receive assistance provided by a nurse home visit, costed using PSSRU unit costs (£53.00).[45]

Additionally, there were some discrepancies between clinical experts consulted by the EAG and the resources used in the CS. Therefore, a number of additional scenarios analyses were requested during clarification. Clinical experts to the EAG also noted that while trialling patients on dupilumab, full blood monitoring would be conducted on a three to six-monthly basis during the trial period (first year of treatment). The company stated that there are no requirements for blood monitoring specified in the SmPC for dupilumab and they would not expect blood counts to be requested every three months. The EAG notes that while they consider there to be uncertainty regarding any additional monitoring required in the first year of treatment, the company's scenario analysis applying three-monthly blood counts had a minimal impact on the ICER (<£40).

Clinical experts also noted that the frequency of spirometry tests used as part of health state resource use were optimistic as in current clinical practice mild/moderate patients would be unlikely to receive spirometry and severe/very severe COPD patients may receive spirometry once annually. The company noted that frequencies used in the base-case were sourced from the NICE COPD guidelines model (NG115) and reflected the guidance committee's opinion.[7] The EAG is aware that variability in clinical practice and pressures on NHS service availability may influence differences in opinion/experiences between experts. The EAG notes that the additional scenario requested by the EAG in light of clinical expert opinion had a minor influence on the ICER and therefore no changes have been made by the EAG.

The company used an analysis of HES data to inform resource use associated with severe exacerbations. During clarification, the company clarified that oral corticosteroids and antibiotics are not costed separately for severe exacerbations as they are assumed to be included in the cost of a hospital stay. It was also noted that the company applied the average cost of a hospital stay for each severe exacerbation, as opposed to the cost being based on the average length of stay estimated from the HES analysis (2.9 days). The EAG notes that as more severe exacerbations are experienced in the background therapy only arm, this approach will favour dupilumab. Lastly, the proportion of patients attending follow-up appointments were reported for both 30 days (18%) and 90 days (37%). The EAG notes that the 18% of patients followed up within 30 days are also included in the 37% followed up at 90 days and therefore consider it more appropriate to only apply costs to the 37% to avoid double counting. This was requested as a scenario during clarification and is implemented in the EAG's preferred analyses and has a minimal impact on the ICER.

For clarity, the resource use and cost codes applied from the NHS Reference Costs 2022/23[47] used for severe exacerbations in the EAG's preferred analysis are shown below.

Table 43. Resource use and cost codes applied in EAG preferred analysis for severe exacerbations

Resource	Proportion of patients per severe exacerbation	Unit costs	Unit cost source
Ambulance transport	70%	£244.09	Weighted average of all ambulance events.
A&E admission	88%	£312.49	Weighted average of admitted Emergency Medicine entries, Consultant led emergency department, Service code 01 (excluding dental).
Hospital stay episode*	100%	£3,239.40	Weighted average of Chronic Obstructive Pulmonary Disease or Bronchitis: Non-elective long stay,

			excluding one day or less category. Currency codes DZ65A-DZ65J.
ICU (length of stay, days)	0.01	£2,330.22	Weighted average of all non-specific, general adult critical care bed days. Service code CCU01.
Readmission within 30 days	14%	£3,239.40	Weighted average of Chronic Obstructive Pulmonary Disease or Bronchitis Non-elective long stay, excluding one day or less category. Currency codes DZ65A-DZ65J.
Ventilation	7%	£1,080.62	Non-elective, non-invasive ventilation, 19 years and over. Currency code DZ37A–DZ37B.
Oxygen therapy	2%	£265.57	Non-elective oxygen assessment and monitoring. Currency code DZ38Z.
CT scan	10%	£114.61	Weighted average of Diagnostic Imaging Service: Directly access CT scans, excluding 18 years and under.
Echocardiogram	5%	£91.60	Diagnostic Imaging Service: Directly accessed, Simple echocardiograms, 19 years and over.
CPAP therapy	1%	£1,080.62	Weighted average of Non-elective, non-invasive ventilation, 19 years and over, long and short stay.
Follow-up outpatient appointments within 90 days of exacerbation	37%	£166.77	Weighted average of Respiratory medicine service: Non-admitted follow-up outpatient attendances (consultant led and non-consultant led). Currency codes WF01A and WF01C.
Total annual cost		**£4,331.58**	

*The EAG notes that the CS incorrectly states 1 day instead of applying cost of episode to all severe exacerbations.

Abbreviations: A&E, accident and emergency; CPAP, continuous positive airway pressure; CT, computed tomography; ICU, intensive care unit.

5 Cost effectiveness results

5.1 Company's cost effectiveness results

Table 44 presents the cost-effectiveness results of the company's updated (i.e. post clarification) base case deterministic and probabilistic analyses dupilumab plus background therapy. The company performed a probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around base case results. Incremental results from the company's PSA are based on 1,000 simulations.

In the base case probabilistic analysis, an incremental quality-adjusted life-year (QALY) gain of [redacted] over background therapy along with increased costs of [redacted] for dupilumab plus background therapy generates an incremental cost-effectiveness ratio (ICER) of £23,624. The net health benefit (NHB) based on the deterministic results using the £20,000 and £30,000 threshold is [redacted] and [redacted], respectively. A positive NHB implies that overall population health would be increased because of the new intervention.

Table 44. Updated (post clarification) company base case results

Interventions	Total Costs (£)	Total LY	Total QALYs	Δcosts (£)	ΔLYs	Δ QALYs	ICER (£/QALY)
Deterministic results							
Background Therapy	[redacted]	[redacted]	[redacted]	-	-	-	-
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25,515
Probabilistic results							
Background Therapy	[redacted]	[redacted]	[redacted]	-	-	-	
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	23,624

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

A PSA scatterplot is presented in Figure 13 and a cost-effectiveness acceptability curve (CEAC) is presented in Figure 14. Based on these analyses, the probability that dupilumab plus background therapy is cost effective versus background therapy alone is approximately 5% at a willingness to pay (WTP) threshold of £20,000 and approximately 96% at a WTP threshold of £30,000.

Figure 13. Scatterplot of PSA estimates (Figure 14 of the company's additional clarification response document)

Figure 14. Cost-effectiveness acceptability curve (Figure 15 of the company's clarification response)

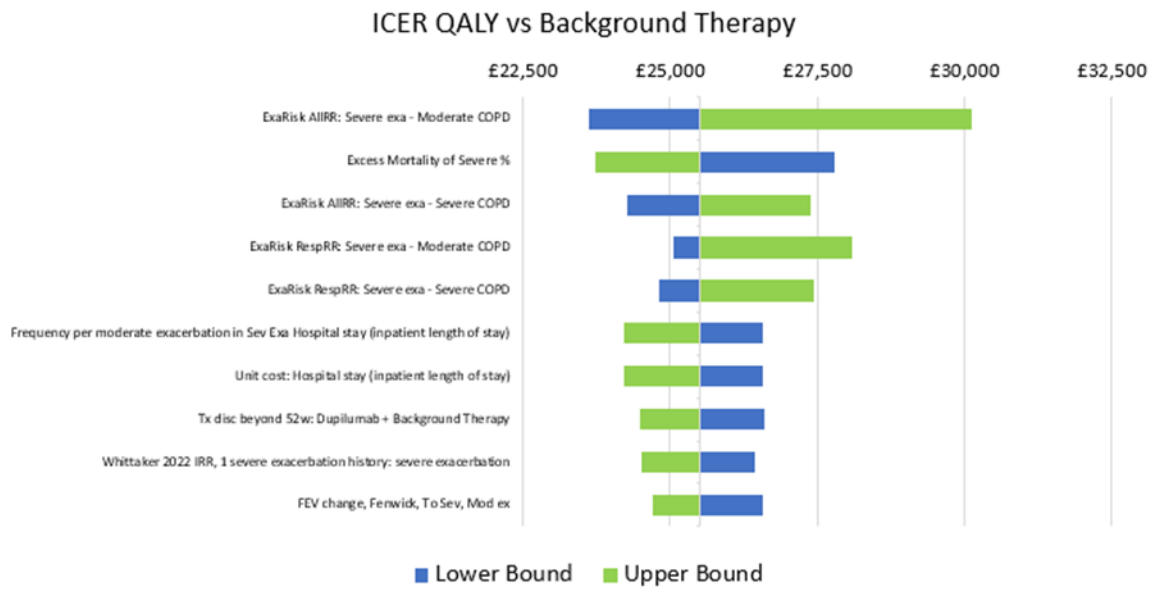
5.2 Company's sensitivity analyses

5.2.1 One-way sensitivity analysis

The company conducted one-way sensitivity analyses (OWSAs) to assess the impact on the ICER of varying specific parameters in isolation and to identify the main model drivers. The results are illustrated in the tornado diagrams presented in Figure 15.

The ICER was most sensitive to the rate ratios of severe exacerbations in the moderate and severe COPD severity health states, representing the treatment effect, and the excess mortality applied for severe exacerbations.

Figure 15. Tornado plot (Figure 16 of the company clarification response)



5.2.2 *Scenario analysis*

The company undertook an extensive series of scenario analyses to assess the impact of applying alternative assumptions to key model parameters, presented in Table 45. In addition, the company conducted several additional scenario analyses requested by the EAG, also presented in the tables below.

Table 45. Company scenario analysis (reproduced from Table 62 of the company clarification response)

No.	Scenario	Deterministic results			Probabilistic results		
		Δcosts (£)	Δ QALYs	ICER (£/QALY)	Δcosts (£)	Δ QALYs	ICER (£/QALY)
0	**Company base case**	[redacted]	[redacted]	**25,515**	[redacted]	[redacted]	**23,518**
1	Discount rate - 3% for costs and outcomes	[redacted]	[redacted]	25,975	[redacted]	[redacted]	24,292
2	Discount rate - 5% for costs and outcomes	[redacted]	[redacted]	24,257	[redacted]	[redacted]	22,480
3	Time horizon - 5 years	[redacted]	[redacted]	59,894	[redacted]	[redacted]	54,948
4	Time horizon - 10 years	[redacted]	[redacted]	33,910	[redacted]	[redacted]	31,296
5	Time horizon - 20 years	[redacted]	[redacted]	25,853	[redacted]	[redacted]	24,274
6	Annual discontinuation rate beyond 52 weeks – 22.4%	[redacted]	[redacted]	22,832	[redacted]	[redacted]	20,889
7	Annual discontinuation rate beyond 52 weeks – 25.84%	[redacted]	[redacted]	21,873	[redacted]	[redacted]	19,885
8	FEV1 treatment effect duration - Dupilumab + background therapy - 1 years; background therapy - 0 year	[redacted]	[redacted]	27,704	[redacted]	[redacted]	25,391
9	Baseline exacerbation rate - Background therapy - RWE; Dupilumab + background therapy - RR vs background therapy alone	[redacted]	[redacted]	25,769	[redacted]	[redacted]	23,731
10	Baseline exacerbation rate - Background therapy – Pooled BOREAS and NOTUS (taken during the trial); Dupilumab + background therapy - RR vs background therapy alone	[redacted]	[redacted]	28,738	[redacted]	[redacted]	27,836
11	Markov transition probabilities (transitions related to exacerbation) - Background therapy - Pooled BOREAS and NOTUS; Dupilumab + background therapy - RR vs background therapy alone With pooled ITT baseline exacerbation taken during the trial	[redacted]	[redacted]	46,244	[redacted]	[redacted]	46,895
12	Utilities - Mean adjusted CFB (LS-Regression-CW-NOTUS) for COPD as well as exacerbation disutilities	[redacted]	[redacted]	26,100	[redacted]	[redacted]	24,040
13	Utilities - Spencer *et al*. 2005 & Sadatsafavi *et al*. 2019 with exacerbation disutilities from Rutten Van Molken *et al*. 2009.[21, 40, 41]	[redacted]	[redacted]	26,784	[redacted]	[redacted]	24,391

14	Utilities - Rutten Van Molken *et al*. 2006 with exacerbation disutilities from Rutten Van Molken *et al*. 2009.[19, 41]	[redacted]	[redacted]	25,294	[redacted]	[redacted]	23,393
15	Utilities - Borg *et al*. 2004 with exacerbation disutilities from Rutten Van Molken *et al*. 2009.[20, 41]	[redacted]	[redacted]	24,642	[redacted]	[redacted]	22,426
16	Excess mortality due to GOLD severity - Shavelle *et al*. 2009.[48]	[redacted]	[redacted]	25,683	[redacted]	[redacted]	23,589
17	Excess mortality due to GOLD severity - Leivseth *et al*. 2013.[49]	[redacted]	[redacted]	25,810	[redacted]	[redacted]	23,467
18	Excess mortality due to exacerbation - Whittaker *et al*. 2022.[1]	[redacted]	[redacted]	36,449	[redacted]	[redacted]	33,331
19	FEV1 treatment effect beyond the trial - Unadjusted FEV_1 trajectory according to Fenwick	[redacted]	[redacted]	26,970	[redacted]	[redacted]	24,481
20	Societal impact - Include societal perspective comprising loss of productivity and early retirement for patients only	[redacted]	[redacted]	25,635	[redacted]	[redacted]	24,345
EAG requested scenarios							
B10	GOLD stage proportions at baseline specific to each treatment arm	[redacted]	[redacted]	£25,530	[redacted]	[redacted]	£23,862
B11	Removal of 'trial effects' on FEV_1	[redacted]	[redacted]	£24,811	[redacted]	[redacted]	£23,635
B12	No difference in severe exacerbation rate between treatment arms	[redacted]	[redacted]	£61,457	[redacted]	[redacted]	£55,427
B18	No treatment effect maintenance period	[redacted]	[redacted]	£31,488	[redacted]	[redacted]	£28,914
B20	No difference in event rates in non-fatal CV events between treatment arms	[redacted]	[redacted]	£25,638	[redacted]	[redacted]	£23,866
B22	Removal of CFR applied to severe exacerbations	[redacted]	[redacted]	£49,954	[redacted]	[redacted]	£51,884
B25	Removal of COVID-19 related discontinuations to trial based discontinuation rate (8.5%)	[redacted]	[redacted]	£25,483	[redacted]	[redacted]	£23,827
B26	Non-treatment specific utility valued used (sourced from Spencer et al 2005 & Sadatsafavi et al 2019)	[redacted]	[redacted]	£26,784	[redacted]	[redacted]	£24,780
B27	Mapped SGRQ to EQ-5D-3L, removing non-significant variables	[redacted]	[redacted]	£27,237	[redacted]	[redacted]	£25,179
B29	CV event disutilities from Ara and Brazier, 2010	[redacted]	[redacted]	£25,232	[redacted]	[redacted]	£23,323
B31	Chronic disutility of exacerbations (12 months) sourced from Jackson *et al.* 2024	[redacted]	[redacted]	£27,074	[redacted]	[redacted]	£25,408
B32	5% of patients receive support with dupilumab administration (outpatient attendance)	[redacted]	[redacted]	£26,680	[redacted]	[redacted]	£24,796

B33	Dupilumab patients receive three-monthly full blood count during the first year of treatment	[redacted]	[redacted]	£25,553	[redacted]	[redacted]	£23,732
B34	Spirometry only applied to patients in severe/very severe COPD health state, once annually	[redacted]	[redacted]	£25,478	[redacted]	[redacted]	£23,689
B36	37% of severe exacerbation patients followed up after 90 days (i.e. removal of the 18% of patients followed up after 30 days)	[redacted]	[redacted]	£25,543	[redacted]	[redacted]	£23,753

Abbreviations: CFB, change from baseline; CFR, case fatality rate; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; CW, crosswalk; EAG, External Assessment Group; EQ-5D-5L, EuroQoL 5-Dimensions 5-Level; FEV1, forced expiratory volume in 1 second; ICER, incremental cost-effectiveness ratio; ITT, intent-to-treat; LS, least squares; N/A, not applicable; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life-year; RR, risk ratio; RWE, real world evidence; UK, United Kingdom

5.3 Model validation and face validity check

Section B.3.14 in the company submission outlines the company's approach to the validation of the economic model, which included validation checks by an external company. The EAG notes that a number of model errors were identified by either the EAG or the company during the clarification stage that had not been during the company's initial validation. These errors were amended during the clarification process.

6 Additional economic analysis undertaken by the EAG

6.1 Model corrections

Following the clarification stage, the EAG identified a further model error which resulted in the age used for applying general population utility adjustments to be incorrect following a change in the selected utility source. This was amended in both the company's and EAG model. Both the company and EAG checked the results of all previously presented scenarios and found this had not impacted any results.

6.2 Exploratory and sensitivity analyses undertaken by the EAG

As discussed in Section 4, the EAG identified a number of uncertainties that warranted further exploration in scenario analyses, in addition to the company's own sensitivity and scenario analyses. The majority of these were conducted by the company in response to clarification, as previously shown in Table 45 in Section 5.2.2. The additional scenarios performed by the EAG are detailed below.

1. Trial based analysis in which both the baseline exacerbation rates and the Markov exacerbation transition probabilities for each treatment arm are based on data derived directly from the trial population. The exacerbation transition probabilities are based on the pooled BOREAS and NOTUS trial data rather than the application of a relative risk (Section 4.2.4).
2. No further adjustment of the reference exacerbation rate from Whittaker *et al.* 2022,[2] used to estimate the future number of exacerbations, for patients who had no exacerbations in the previous year. This scenario does not apply any adjustments from Wallace *et al.* 2019[25] and therefore the reference rate does not differ between GOLD severity stages (Section 4.2.4.3).
3. Long-term discontinuation rate of dupilumab equivalent to that observed during the trial period; 9.3% (Section 4.2.6).
4. Utility values for COPD health states and exacerbation disutility equivalent to committee preferences in TA461 (Section 4.2.9.4).[8]
5. 5% of patients receive assistance with dupilumab administration, provided by a nurse home visit (Section 4.2.10.4).

6. Separate standardised mortality rates (SMRs) for each COPD severity health state by treatment arm informed by data from the IMPACT clinical trial for double/triple background therapy. This scenario was originally conducted by the company during clarification, however, the EAG notes that it was conducted incorrectly in the company's analysis (Section 4.2.7.1).
7. Treatment benefit of dupilumab on severe exacerbations is halved. This is an illustrative example only to explore the impact of a reduced treatment effect on severe exacerbations due to the uncertainty from the pooled NOTUS and BOREAS trials, which showed no statistically significant difference in severe exacerbations. This illustrative example applies an arbitrary adjustment to the rate ratio inputs used to derive dupilumab annual exacerbation rates (Section 4.2.5.3).

6.3 EAG scenario analysis

Table 46 presents the results of the EAG exploratory analyses described in Section 6.2. Results reported include the company's proposed patient access scheme (PAS) discount on the list price of [redacted] for dupilumab.

The EAG notes that as not all of the following scenarios were implemented in the model probabilistically, all results presented below are deterministic. The EAG notes that the company's probabilistic results were often lower (£1000–£2000) than the deterministic values, mainly driven by differences in life years, but in line with one another.

Table 46. Results of the EAG's scenario analyses (deterministic)

	Results per patient	Dupilumab + background therapy	Background therapy only	Incremental value
0	Company base case			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			£25,515
1	Full trial-based analysis			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			£46,680
2	No adjustment to Whittaker *et al.* reference exacerbation rate			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]

	ICER (£/QALY)			£31,775
3	Dupilumab long-term discontinuation equal to observed trial period discontinuation			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			£28,351
4	TA461 committee preference utility values for COPD health state and exacerbation disutility			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			£25,113
5	Dupilumab administration support via nurse home visit (5%)			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			£25,830
6	Treatment arm specific SMRs			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			£35,607
7	Dupilumab treatment benefit on severe exacerbations is halved			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			£36,629

Abbreviations: COPD, chronic obstructive pulmonary disease; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SMR, standardised mortality rate; TA, technology appraisal.

6.4 EAG preferred assumptions

In this section, the EAG presents its preferred analysis for the cost-effectiveness of dupilumab plus background therapy for the treatment of people with uncontrolled COPD with raised blood EOS. The assumptions that form the EAG's preferred base case are listed below, with cumulative results of each analysis shown in Table 47. The EAG notes that the individual impact of each scenario on the company's base-case ICER has been previously presented in either Table 45 or Table 46. The EAG ran probabilistic results over 1,000 iterations. It is noted that due to variability in the PSA, there may be small discrepancies in the incremental costs or QALYs between scenarios.

- Starting distribution of patients in each GOLD stage removes any 'trial effects' on FEV_1;
- Annual transition probabilities to more severe COPD states are based on Fenwick *et al.* 2021, with no additional adjustment of a multiplier for EOS≥300;

- No difference in event rates in non-fatal CV events between treatment arms;
- Non-treatment specific utility values, informed by trial data of mapped SGRQ to EQ-5D-3L (cross-walked) using statistically significant variables only. Disutilities for exacerbations are also based on the same trial-based analysis;
- Cardiovascular event disutilities informed by Ara and Brazier 2010;[3]
- 5% of patients receive assistance with dupilumab administration, provided by a nurse home visit;
- 37% of severe exacerbation patients followed up after 90 days (i.e. removal of the 18% of patients followed up after 30 days in resource use);
- No additional excess mortality due to severe exacerbations.

As shown in Table 47, implementing the EAG's preferred assumptions results in a probabilistic ICER of £73,154 per QALY gained. The main driver of the ICER is the removal of excess mortality rate for severe exacerbations.

Table 47. EAG's preferred model assumptions, cumulative ICER (probabilistic)

Preferred assumption	Section in EAG report	Cumulative incremental costs	Cumulative incremental QALYs	Cumulative ICER (£/QALY)
Company base case post clarification	Section 5.1	[redacted]	[redacted]	£23,624
Removal of FEV_1 trial effects	Section 4.2.5	[redacted]	[redacted]	£23,597
COPD severity transition probabilities based on Fenwick *et al.* with no further multiplier applied	Section 4.2.4.3	[redacted]	[redacted]	£24,896
No difference in event rates in non-fatal CV events between treatment arms	Section 4.2.8	[redacted]	[redacted]	£24,816
Utility value informed by mapping of SGRQ from pooled BOREAS and NOTUS trials to EQ-5D-3L, analysis excluding non-significant covariates.	Section 4.2.9.4	[redacted]	[redacted]	£26,504
CV event disutilities informed by Ara and Brazier 2010	Section 4.2.9.4	[redacted]	[redacted]	£26,129
Dupilumab administration support via nurse home visit (5%)	Section 4.2.10.4	[redacted]	[redacted]	£26,353

37% of severe exacerbation patients followed up after 90 days only	Section 4.2.10.4	[redacted]	[redacted]	£26,382
No excess mortality due to severe exacerbations	Section 4.2.7.1	[redacted]	[redacted]	£73,154
EAG preferred base case	**-**	[redacted]	[redacted]	**£73,154**

Abbreviations: COPD, chronic obstructive pulmonary disease; CV, cardiovascular; EAG, External Assessment Group; EQ-5D-3L, European Quality of Life 5 Dimensions 3 Level Version; FEV_1, forced expiratory volume in one second; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Full probabilistic and deterministic EAG base case analysis results are shown below in Table 48. The EAG notes that the probabilistic ICER is ≈£5000 higher than the deterministic results. This is a result of small differences in the absolute QALYs having a larger impact on the ICER.

Table 48. EAG base case results

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Dupilumab + background therapy	[redacted]	[redacted]	[redacted]	-	-	-	-
Background therapy only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£68,832
Probabilistic results							
Dupilumab + background therapy	[redacted]	[redacted]	[redacted]	-	-	-	-
Background therapy only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£73,154

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

6.5 EAG additional sensitivity analysis

The following additional sensitivity analyses were also undertaken using the EAG's preferred analysis to explore the sensitivity to alternative assumptions:

1) Full trial-based analysis – Section 4.2.4.1 and Section 4.2.5.1;

2) Treatment effect maintenance period equal to:

    a) One year, i.e. trial period duration;

b) Two years.

The EAG consider the assumption made in both the company and EAG base case of a three-year treatment effect to be optimistic. Therefore, this scenario is included to highlight the impact on the ICER of alternative assumptions – Section 4.2.5.3;

3) Excess mortality related to exacerbations is taken from Whittaker *et al.* 2022[2] (the same source used in the model for informing exacerbation rates based on previous exacerbations). This applies a mortality incidence rate ratio (IRR) based on baseline frequency and severity of exacerbations (whereby no recent exacerbations is used as the reference). If including an excess mortality for exacerbations, the EAG prefers this data source due to the consistency with other key inputs used in the model, but notes that there is still a potential of double counting the mortality impact applied based on COPD severity stage – Section 4.2.7.1;

4) Excess mortality related to exacerbations (severe only) is taken from the latest National Asthma and Chronic Obstructive Pulmonary Disease Audit Programme (NACAP) report[34] which stated that 6.1% of COPD patients died within 30 days of a hospital admission. This scenario is included to provide an alternative estimate of the severe exacerbations only excess mortality CFR than that used by the company – Section 4.2.7.1;

5) No difference in severe exacerbations between treatment arms. The EAG notes that the impact of dupilumab on severe exacerbation rates is uncertain based on a lack of a statistically significant difference between treatment arms observed in the pooled trials and therefore includes this analysis of an illustrative example of the effect – Section 4.2.5.3;

6) Treatment benefit of dupilumab on severe exacerbations is halved. This is an illustrative example only to explore the impact of a reduced treatment effect on severe exacerbations due to the uncertainty from the pooled NOTUS and BOREAS trials, which showed no statistically significant difference in severe exacerbations. This illustrative example applies an arbitrary adjustment to the rate ratio inputs used to derive dupilumab annual exacerbation rates – Section 4.2.5.3;

7) Utility values equivalent to committee preferences in TA461. While the EAG consider the use of mapped SGQR data from the trial to be the most appropriate, it is noted that there are some concerns with the reliability of the mapping analysis due to uncertainty in the correlation between the SGQR and EQ-5D-5L observed in the trial and the low collection timepoints of EQ-5D-5L in the trial – Section 4.2.9.4.[8]

As shown in Table 49, the ICER is sensitive to all the additional scenario analyses conducted by the EAG, highlighting the impact of key uncertainties in the model. The inclusion of excess mortality related to exacerbations (split by severity and frequency) from Whittaker *et al.* 2022, reduced the EAG's preferred ICER to £41,919, which the EAG notes is still considerably higher than the typical NICE threshold of £20-000–£30,000 per QALY gained. Using a lower CFR for excess mortality of 6.1% based on NACAP data also resulted in a similar lower ICER (£38,403). The EAG notes that while the use of alternative utility values did not have a large impact on the ICER when applied to the company's base-case analysis, this is not the case when changed in the EAG's preferred analysis (additional sensitivity analysis 7) due to the alternative assumptions in excess mortality resulting in much lower life years, and consequently QALYs, and therefore small changes in absolute QALYs has a greater impact on the ICER.

Table 49. Results of additional sensitivity analysis around the EAG base case, probabilistic

	Results per patient	Intervention	Comparator	Incremental value
0	EAG base case			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£73,154
1	Full trial-based analysis			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			£92,589
2a	Treatment effect maintenance period equal to one year			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			£137,497
2b	Treatment effect maintenance period equal to two years			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			£94,424
3	Excess mortality related to exacerbations is taken from Whittaker *et al.* 2022			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			£41,919
4	Excess mortality related to severe exacerbations is taken from NACAP report (6.1%)			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]

	ICER (£/QALY)			£38,403
5	No difference in severe exacerbations between treatment arms			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			£101,763
6	Treatment benefit of dupilumab on severe exacerbations is halved*			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			£81,425
7	Utility values equivalent to committee preferences in TA461			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			£52,715

*Due to the arbitrary nature of this scenario, results presented are only available deterministically

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; NACAP, National Asthma and Chronic Obstructive Pulmonary Disease Audit Programme; QALY, quality adjusted life year; TA, technology appraisal

6.6 Conclusions of the cost effectiveness sections

Generally, the EAG considers the company's submitted cost-effective evidence to adhere to the NICE decision problem defined in the NICE final scope. The company compared dupilumab plus background therapy to background therapy only. However, both roflumilast and azithromycin were excluded as standalone comparators which was deemed appropriate by clinical experts who advised the company. This was also confirmed by the EAG's clinical experts and based on the points previously discussed in Section 2.3.3, the EAG agreed with the exclusion of these comparators from the economic analysis.

The inputs and assumptions used in the model in relation to mortality are the key driver of the ICER and consequently are considered to be a key issue in this appraisal. As previously discussed in Section 4.2.7.1, the EAG considers the company's approach of applying an excess mortality rate for severe exacerbations in addition to the hazard rates applied to each COPD severity stage to result in double counting of the impact of COPD on mortality. The EAG's preferred base case analysis therefore removed the excess mortality applied to severe exacerbations, resulting in a probabilistic ICER of £73,154 per QALY gained. The EAG's sensitivity analysis applying the excess mortality for exacerbations from Whittaker *et al.* 2022, the same study used to inform exacerbation rates in the

following model cycle, resulted in an ICER of £41,919 per QALY gained. The EAG considers this option to be more plausible than that used in the company base case and is a consistent data source with other inputs used in the model. However, the EAG is concerned that there is still the potential for double counting when applying these values in addition to the mortality rates associated with each GOLD severity stage.

While the removal of any excess mortality for exacerbations may underestimate the impact of severe exacerbations on mortality and may be considered pessimistic, the EAG notes that the magnitude of the effect of dupilumab on severe exacerbations is also highly uncertain in the model as the trial was not powered to detect this as a key outcome and results were not statistically significant. The EAG also included an illustrative example (additional sensitivity analysis 6) to demonstrate the impact of changing this value; in the scenario the treatment benefit of dupilumab on severe exacerbations was arbitrarily halved, resulting in a deterministic ICER of £81,425 when implemented on the EAG base case.

Based on patients only receiving dupilumab for the 52-week trial period, no data are available on the long-term treatment effect of dupilumab in COPD patients, resulting in high uncertainty in this model input. The EAG apply the same assumption as the company in their preferred base case analysis of a three-year treatment effect maintenance period, which is based on data from dupilumab in asthma patients. Clinical experts noted that this seems a reasonable assumption in light of a lack of data, yet noted that patients with COPD are likely to have more comorbidities than patients with asthma and therefore may experience decline sooner. Therefore, the EAG considers three years to be an optimistic assumption. The EAG's additional sensitivity analyses showed that reducing this time period had a large impact on the EAG's preferred ICER, increasing to £94,424 when set at two years following initiation and £137,497 when set at one year, i.e. the end of the trial period.

While it did not have a substantial impact on the ICER, the EAG considers the company's approach to modelling annual decline in FEV_1 to overestimate the rate at which patients would progress to a more severe COPD health state. Therefore, the EAG preferred to model annual decline in FEV_1 without the application of a multiplier effect for patients with EOS≥300 but notes that this parameter is uncertain.

The EAG also considers the company's base case analysis to overestimate the cost-effectiveness of dupilumab when taken in addition to background therapy. The EAG notes that there are a number of uncertainties in the assumptions and inputs used in the model, as previously discussed, and that all of the EAG's additional sensitivity analyses are higher than the typical NICE willingness-to-pay threshold of £20,000–£30,000 per QALY gained.

7 References

1. Whittaker H, Rothnie KJ, Quint JK. Cause-specific mortality in COPD subpopulations: a cohort study of 339 647 people in England. *Thorax* 2024; **79**: 202-8.
2. Whittaker H, Rubino A, Müllerová H, Morris T, Varghese P, Xu Y, et al. Frequency and Severity of Exacerbations of COPD Associated with Future Risk of Exacerbations and Mortality: A UK Routine Health Care Data Study. *Int J Chron Obstruct Pulmon Dis* 2022; **17**: 427-37.
3. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2010; **13**: 509-18.
4. Sanofi. Dupixent (dupilumab) 300 mg solution for injection in pre-filled pen SmPC - MHRA. Sept 2024.
5. Excellence NIfHaC. Dupilumab for treating severe asthma with type 2 inflammation [TA751]. Technology appraisal guidance. 2021.
6. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2024. Available from: https://goldcopd.org/2025-gold-report/. Date accessed.
7. National Institute for Health and Care Excellence. Chronic obstructive pulmonary disease in over 16s: diagnosis and management. Economic model report (NICE guideline NG115). 2018.
8. National Institute for Health and Care Excellence. Roflumilast for treating chronic obstructive pulmonary disease - Technology appraisal guidance (TA461). 2017.
9. Alqahtani JS, Oyelade T, Aldhahir AM, Mendes RG, Alghamdi SM, Miravitlles M, et al. Reduction in hospitalised COPD exacerbations during COVID-19: A systematic review and meta-analysis. *PLoS One* 2021; **16**: e0255659.
10. Calverley PM. Minimal Clinically Important Difference—Exacerbations of COPD. *COPD: Journal of Chronic Obstructive Pulmonary Disease* 2005; **2**: 143-8.
11. Jones PW. Minimal Clinically Important Differences in Pharmacological Trials. *American Journal of Respiratory and Critical Care Medicine* 2014; **189**.
12. Crim C, Frith LJ, Donohue JF. FEV1 Minimum Important Difference versus Minimal Detectable Difference? In Search of the Unicorn. *American Journal of Respiratory and Critical Care Medicine* 2021; **203**: 1573-6.
13. Jones P. St. George's Respiratory Questionnaire: MCID. *COPD: Journal of Chronic Obstructive Pulmonary Disease* 2005; **2**: 75-9.
14. Jones P, Gelhorn H, Wilson H, Karlsson N, Menjoge S, Mullerova H, et al. Responder Analyses for Treatment Effects in COPD Using the St George's Respiratory Questionnaire. *Chronic obstructive pulmonary diseases* 2017; **2**: 124-31.
15. Leidy NK, Bushnell DM, Thach C, Hache C, Gutzwiller FS. Interpreting Evaluating Respiratory Symptoms™ in COPD Diary Scores in Clinical Trials: Terminology, Methods, and Recommendations. *Chronic obstructive pulmonary diseases* 2022; **9**: 576-90.
16. Tabberer M, Zhu C-Q, Doyle S, Lipson DA. Defining the minimum clinically important difference (MCID) for the evaluating respiratory symptoms in COPD daily diary using global anchors: data from the FULFIL study. *Thorax* 2018; **73**.
17. Martinez FJ, Rabe KF, Calverley PMA, Fabbri LM, Sethi S, Pizzichini E, et al. Determinants of Response to Roflumilast in Severe Chronic Obstructive Pulmonary Disease. Pooled Analysis of Two Randomized Trials. *Am J Respir Crit Care Med* 2018; **198**: 1268-78.
18. Drummond MF, Jefferson T. Guidelines for authors and peer reviewers of economic submissions to the BMJ. *Bmj* 1996; **313**: 275-83.
19. Rutten-van Molken M, Lee TA. Economic modeling in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2006; **3**: 630-4.

20. Borg S, Ericsson A, Wedzicha J, Gulsvik A, Lundback B, Donaldson GC, et al. A computer simulation model of the natural history and economic impact of chronic obstructive pulmonary disease. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2004; **7**: 153-67.
21. Spencer M, Briggs AH, Grossman RF, Rance L. Development of an economic model to assess the cost effectiveness of treatment interventions for chronic obstructive pulmonary disease. *Pharmacoeconomics* 2005; **23**: 619-37.
22. National institute for Health and Care Excellence. Dupilumab for treating moderate to severe chronic obstructive pulmonary disease [ID6235], 2024. Available from: https://www.nice.org.uk/guidance/gid-ta11246/documents/final-scope. Date accessed: December 2024.
23. Hernández Alava M, Pudney S, Wailoo A. Estimating EQ-5D by Age and Sex for the UK. Report by the Decision Support Unit. 2022.
24. NICE. NICE health technology evaluations: the manual (Process and methods [PMG36]), 2022. Available from: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation. Date accessed: 03 Oct 2023.
25. Wallace AE, Kaila S, Bayer V, Shaikh A, Shinde MU, Willey VJ, et al. Health Care Resource Utilization and Exacerbation Rates in Patients with COPD Stratified by Disease Severity in a Commercially Insured Population. *J Manag Care Spec Pharm* 2019; **25**: 205-17.
26. Fenwick E, Martin A, Schroeder M, Mealing SJ, Solanke O, Risebrough N, et al. Cost-effectiveness analysis of a single-inhaler triple therapy for COPD in the UK. *ERJ Open Res* 2021; **7**.
27. Jenkins CR, Jones PW, Calverley PM, Celli B, Anderson JA, Ferguson GT, et al. Efficacy of salmeterol/fluticasone propionate by GOLD stage of chronic obstructive pulmonary disease: analysis from the randomised, placebo-controlled TORCH study. *Respir Res* 2009; **10**: 59.
28. Quanjer PH, Tammeling G, Cotes J, Pedersen O, Peslin R, Yernault J. Lung volumes and forced ventilatory flows. *European respiratory journal* 1993; **6**: 5-40.
29. Tan WC, Bourbeau J, Nadeau G, Wang W, Barnes N, Landis SH, et al. High eosinophil counts predict decline in FEV(1): results from the CanCOLD study. *Eur Respir J* 2021; **57**.
30. Wechsler ME, Ford LB, Maspero JF, Pavord ID, Papi A, Bourdin A, et al. Long-term safety and efficacy of dupilumab in patients with moderate-to-severe asthma (TRAVERSE): an open-label extension study. *Lancet Respir Med* 2022; **10**: 11-25.
31. Mansur AH, Gonem S, Brown T, Burhan H, Chaudhuri R, Dodd JW, et al. Biologic therapy practices in severe asthma; outcomes from the UK Severe Asthma Registry and survey of specialist opinion. *Clinical & Experimental Allergy* 2023; **53**: 173-85.
32. Office for National Statistics (ONS). National life tables – life expectancy in the UK: 2020 to 2022. 2024. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2020to2022. Date accessed: September 9.
33. Hoogendoorn M, Hoogenveen RT, Rutten-van Mölken MP, Vestbo J, Feenstra TL. Case fatality of COPD exacerbations: a meta-analysis and statistical modelling approach. *Eur Respir J* 2011; **37**: 508-15.
34. National Asthma and Chronic Obstructive Pulmonary Disease Audit Programme (NACAP). Clinical outcomes. October 2018 – March 2020. Summary report. 2023.
35. Halpin DMG, Dransfield MT, Han MK, Jones CE, Kilbride S, Lange P, et al. The effect of exacerbation history on outcomes in the IMPACT trial. *Eur Respir J* 2020; **55**.
36. Tan DJ, van Geffen WH, Walters EH. Impact of Triple Therapy vs Dual Bronchodilator Therapy on Mortality Rates in COPD. *CHEST* 2024; **165**: e158-e9.

37. Kunisaki KM, Dransfield MT, Anderson JA, Brook RD, Calverley PMA, Celli BR, et al. Exacerbations of chronic obstructive pulmonary disease and cardiac events. A post hoc cohort analysis from the SUMMIT randomized clinical trial. *Am J Respir Crit Care Med* 2018; **198**: 51-7.
38. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual. 2022.
39. Hernández Alava M, Wailoo A, Pudney S, Gray L, Manca A. Mapping clinical outcomes to generic preference-based outcome measures: development and comparison of methods. *Health Technol Assess* 2020; **24**: 1-68.
40. Sadatsafavi M, Ghanbarian S, Adibi A, Johnson K, FitzGerald JM, Flanagan W, et al. Development and validation of the Evaluation Platform in COPD (EPIC): a population-based outcomes model of COPD for Canada. *Medical decision making : an international journal of the Society for Medical Decision Making* 2019; **39**: 152-67.
41. Rutten-van Mölken MP, Hoogendoorn M, Lamers LM. Holistic preferences for 1-year health profiles describing fluctuations in health: the case of chronic obstructive pulmonary disease. *Pharmacoeconomics* 2009; **27**: 465-77.
42. Sterne JA, Bodalia PN, Bryden PA, Davies PA, Lopez-Lopez JA, Okoli GN, et al. Oral anticoagulants for primary prevention, treatment and secondary prevention of venous thromboembolic disease, and for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis and cost-effectiveness analysis. *Health Technol Assess* 2017; **21**: 1-386.
43. Hoogendoorn M, Rutten-van Mölken MP, Hoogenveen RT, Al MJ, Feenstra TL. Developing and applying a stochastic dynamic population model for chronic obstructive pulmonary disease. *Value in health* 2011; **14**: 1039-47.
44. Jackson D, Jenkins M, de Nigris E, Purkayastha D, Patel M, Ouwens M. Associations between the EQ-5D-5L and exacerbations of chronic obstructive pulmonary disease in the ETHOS trial. *Qual Life Res* 2024; **33**: 1029-39.
45. Jones K, Weatherly H., Birch S, Castelli A, et al. Unit Costs of Health and Social Care 2023 Manual. 2024. Available from: https://kar.kent.ac.uk/105685/1/The%20unit%20costs%20of%20health%20and%20social%20care_Final3.pdf. Date accessed: 1 October 2024.
46. National Institute for Health and Care Excellence (NICE). British National Formulary (BNF). Last updated: 2 October 2024. 2024.
47. NHS England. National Schedule of NHS Costs Year 2022/23. National Cost Collection Data Publication.
48. Shavelle RM, Paculdo DR, Kush SJ, Mannino DM, Strauss DJ. Life expectancy and years of life lost in chronic obstructive pulmonary disease: findings from the NHANES III Follow-up Study. *Int J Chron Obstruct Pulmon Dis* 2009; **4**: 137-48.
49. Leivseth L, Brumpton BM, Nilsen TIL, Mai X-M, Johnsen R, Langhammer A. GOLD classifications and mortality in chronic obstructive pulmonary disease: the HUNT Study, Norway. *Thorax* 2013; **68**: 914-21.

Single Technology Appraisal

Dupilumab for treating moderate to severe chronic obstructive pulmonary disease [ID6235]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 27 January 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Discrepancy in deterministic results of the EAG's scenario 4 analysis (Table 46)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Discrepancy in the results for deterministic scenario 4 "TA461 committee preference utility values for COPD health state and exacerbation disutility". "Incremental Value: • Total costs (£): £[redacted] • QALYs: [redacted] • ICER (£/QALY): £25,113" Table 46, Page 119	We identified a result discrepancy when we performed the same scenario detailed by the EAG. Instead of an incremental cost of £[redacted], incremental QALY of [redacted] and an ICER of £25,113. We calculated an ***incremental total cost of*** [redacted], ***incremental QALY of*** [redacted] and an ***ICER of £25,294***.	Although the difference is small, ensuring accuracy is important to support decision-making. Addressing this will help ensure the report remains transparent and aligns with high standards of reproducibility and reliability.	This is not a factual inaccuracy; no change is required. The EAG notes that the ICER obtained by the company (£25,294) does not include changes to the exacerbation disutilities, whereas the EAG's scenario does. This was applied by setting cell F28 in sheet "Scenarios_RecommendedbyEAG" in the EAG version of the company's model to 1 and ensuring the changes listed are made.

Issue 2 Clarification on EAG's additional sensitivity analysis results (Table 49)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Upon initial review, the results of the additional sensitivity analysis (Table 49) appear to be cumulative results starting from the EAG's preferred ICER. The company replicated the scenarios and obtained similar results (since deterministic results were not provided). However, the ICERs for scenarios 4 and 5 dropped significantly, and the company could only achieve comparable results if the scenarios were not cumulative. Table 49, Page 123 -124	We propose that further clarification be provided in Table 49, including the base case ICER used to derive the results, the deterministic results, and whether the scenarios are isolated or cumulative.	Addressing this will help ensure the report remains transparent and aligned with high standards of reproducibility and reliability.	This is not a factual inaccuracy; no change is required. As stated in the title for Table 49, the results provided are based on 'additional sensitivity analysis around the EAG base case'. The EAG notes that these are not cumulative ICER's but separate scenarios applied to the EAG base case. Due to the NICE methods guide stating that scenario analyses should also be presented probabilistically, the EAG only presents probabilistic results. As some of the additional scenarios included in Table 49 result in small QALY gains (for example, scenario 2a), the probabilistic ICER is higher than the deterministic, which may explain why the company was unable to replicate results. The EAG notes that in order for the company to replicate the results,

			they will need to run each scenario probabilistically. The EAG does not consider the inclusion of deterministic results to the report necessary and therefore no changes have been made. However, for transparency, the EAG has provided the model for scenario 2a in which there is a larger difference between deterministic and probabilistic results, as an example.

Issue 3 Inaccurate reporting of TEAEs due to COVID-19

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Inaccuracy in the proportion of patients reported to have TEAEs due to COVID-19. "However, the EAG notes that over 10% of patients reported TEAEs due to COVID-19 and any impact of this on their response to	We propose that this sentence should be removed.	In the pooled analysis, 9.0% of patients treated with dupilumab and 8.8% of patients treated with placebo reported TEAEs due to COVID-19 (based on SMQ 20000237 COVID-19; page 119 of	Thank you for highlighting this factual inaccuracy. The EAG report has been updated to reflect the correct percentages who reported TEAEs due to COVID-19 in each arm.

treatment should be considered." Page 16		Sanofi 2023 Summary Safety Pooled analysis).	
Inaccuracy in the proportion of patients reported to have TEAEs due to COVID-19. "Over 10% of patients reported treatment-emergent adverse events (TEAEs) due to COVID-19, and so it is important to consider whether this could have affected either the severity of their COPD, or their response to treatment" Page 44	We propose that the sentence be rephrased as follows: "***Although less than*** 10% of patients reported treatment-emergent adverse events (TEAEs) due to COVID-19, it is important to consider whether this could have affected either the severity of their COPD, or their response to treatment"	In the pooled analysis, 9.0% of patients treated with dupilumab and 8.8% of patients treated with placebo reported TEAEs due to COVID-19 (based on SMQ 20000237 COVID-19; page 119 of Sanofi 2023 Summary Safety Pooled analysis).	

Issue 4 Recognition of the 2025 GOLD Strategy update, which further specifies distinct populations recommended for roflumilast and azithromycin

Description of problem	Description of proposed amendment	Justification for amendment	EAG response

The EAG correctly report the use of roflumilast and azithromycin in current practice. However, the GOLD 2025 Strategy further defines the recommended populations for these treatments, which should be noted. "The final stage in the treatment pathway for patients who continue to experience exacerbations following triple therapy is the option of add-on therapy. In current practice, add-on therapy consists of two options: 1. Roflumilast for patients with severe COPD (FEV_1<50%) and chronic bronchitis with ≥2 exacerbations in the previous year; or 2. Azithromycin as an off-label option for non-smokers with significant daily sputum production	We propose the following sentence should be added at the end of this paragraph: "***Additionally, the GOLD 2025 Strategy now recommends that add-on therapy with roflumilast or azithromycin is recommended for patients with EOS < 300 cell/µL."***	For patients treated with LABA + LAMA + ICS who still have exacerbations, the GOLD 2025 Strategy now recommends roflumilast and azithromycin treatment options for distinct patient populations, also defined with EOS < 300 (distinct from where dupilumab is recommended): • Among those who are not currently smoking, consider adding azithromycin. Consideration to the development of resistant organisms should be factored into decision-making. [Figure 3.9 clearly places azithromycin in patients with blood EOS < 300].	This is not a factual inaccuracy; no change is required. The 300 cells/µl threshold is not currently reflected in the NICE guidelines.

and ≥4 exacerbations per year, prolonged exacerbations, or exacerbations resulting in hospitalisation." Page 28		• Among those with FEV_1<50%, symptoms of chronic bronchitis and history of severe exacerbation, consider adding roflumilast. [Figure 3.9 clearly places roflumilast in patients with blood EOS < 300].	

Issue 5 Incomplete description of the burden of COPD exacerbations

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Incomplete description of the burden of exacerbations; the impact of exacerbations on lung function decline is not captured. "People who experience exacerbations more frequently tend to	We propose that the sentence be rephrased as follows: "People who experience exacerbations more frequently tend to experience a higher number of cardiovascular events, ***faster lung function decline*** and have a higher symptom burden than those	There is published evidence to support that COPD exacerbations are associated with more rapid lung function decline (progression). For example: • Kerkhof M, Voorham J,	Thank you for highlighting this factual inaccuracy. The proposed amendment has been added to the report.

experience a higher number of cardiovascular events and have a higher symptom burden than those who have less frequent exacerbations” Page 25	who have less frequent exacerbations”	Dorinsky P, et al. Association between COPD exacerbations and lung function decline during maintenance therapy. *Thorax*. 2020;75(9):744-753. doi:10.1136/thoraxjnl-2019-214457 • Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease [published correction appears in Thorax. 2008 Aug;63(8):753]. *Thorax*. 2002;57(10):847-852.	

		doi:10.1136/thorax.57.10.847	

Issue 6 Population wording

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
We thank the EAG for adopting the revised population wording of *'uncontrolled COPD with raised blood eosinophils*' to align with our marketing authorization. However, there were a few instances in the EAG report where 'moderate to severe COPD' was used to describe the population of interest: • "Without further evidence assessing the change required to represent a clinically meaningful difference in patients with moderate to severe	The statements should be rewritten as: • Without further evidence assessing the change required to represent a clinically meaningful difference in patients with ***uncontrolled COPD characterised by raised blood eosinophils***, it is difficult to confidently use the 100 ml threshold to assess the effects of dupilumab in this population (page 48) • The EAG notes that although the population of interest for dupilumab is patients with ***uncontrolled COPD characterised by raised***	The definition 'Adults with uncontrolled COPD (≥2 moderate or ≥1 severe historical exacerbations within 12 months) with raised blood eosinophils (EOS ≥300 cells/μL), on triple therapy (LABA + LAMA + ICS) or double therapy (LABA + LAMA) if ICS is not appropriate' matches the marketing authorisation for dupilumab.	Thank you for highlighting this factual inaccuracy. The definition used in the EAG report has been updated to "uncontrolled COPD with raised blood EOS".

COPD, it is difficult to confidently use the 100 ml threshold to assess the effects of dupilumab in this population" (page 48) • "The EAG notes that although the population of interest for dupilumab is patients with moderate to severe COPD, 1.9% were classified as mild at baseline." (page 72) • "In this section, the EAG presents its preferred analysis for the cost-effectiveness of dupilumab plus background therapy for the treatment of people with moderate to severe chronic obstructive pulmonary disease	***blood eosinophils***, 1.9% were classified as mild at baseline. (page 72) • In this section, the EAG presents its preferred analysis for the cost-effectiveness of dupilumab plus background therapy for the treatment of people ***uncontrolled COPD characterised by raised blood eosinophils***. (page 119)		

(COPD).” (page 119)			

Issue 7 Clarification of terminology for nurse home visits

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The report refers to “nurse care home visit,” which could be misinterpreted as implying that the homecare company delivering dupilumab provides nurses for the service. This is unclear and potentially misleading. • “5% of patients receive assistance with dupilumab administration, provided by a nurse home care visit” (Page 23) • “Dupilumab administration support	We propose updating the wording to ***“nurse home visit***” to clearly indicate that the administration is performed by nurses visiting patients’ homes. • “5% of patients receive assistance with dupilumab administration, provided by ***nurse home visit***” (Page 23) • “Dupilumab administration support via ***nurse home visit*** (5%)” (Page 23) • “In the EAG preferred base-case it is assumed that 5% of patients receive assistance provided by ***nurse home visit***, costed using PSSRU unit costs (£53.00).” (Page 107)	Dupilumab will be delivered through homecare services, funded directly by Sanofi. Therefore, the phrase ‘home care nurse’ could be misinterpreted to suggest that the company is financially responsible for the nursing services provided, when in fact, these will be delivered by NHS nurses. Clarifying this and making this amendment eliminates ambiguity, ensuring the description accurately reflects the scenario.	Thank you for highlighting this factual inaccuracy. The proposed amendments have been made to the EAG report.

via home care nurse (5%)" (Page 23) • "In the EAG preferred base-case it is assumed that 5% of patients receive assistance provided by a nurse home visit, costed using PSSRU unit costs (£53.00)." (Page 107) • "5% of patients receive assistance with dupilumab administration, provided by a nurse home care visit" (Page 117) • "Dupilumab administration support via home care nurse (5%)" (Page 119) • "5% of patients receive assistance with dupilumab administration, provided by a nurse	• "5% of patients receive assistance with dupilumab administration, provided by ***nurse home visit***" (Page 117) • "Dupilumab administration support via ***nurse home visit*** (5%)" (Page 119) • "5% of patients receive assistance with dupilumab administration, provided by ***nurse home visit***" (Page 120) • "Dupilumab administration support via ***nurse home visit*** (5%)" (Page 121)		

home care visit” (Page 120) • “Dupilumab administration support via home care nurse (5%)” (Page 121)			

Issue 8 Description of overestimation of treatment effects based on interim analyses of clinical trials

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG notes that interim analyses (NOTUS trial) can overestimate treatment effects. We would like to point out that this could also result in an underestimation of treatment effects. "However, interim analyses can have drawbacks including the potential overestimation of treatment effects, which should be considered when interpreting the results of the NOTUS study." Page 43	We propose that the sentence be modified to: "However, interim analyses can have drawbacks including the potential ***underestimation or overestimation*** of treatment effects, which should be considered when interpreting the results of the NOTUS study."	It is unreasonable to only note the possibility of "overestimation" when "underestimation" is just as likely, when describing uncertainty.	This is not a factual inaccuracy; no change is required. Thank you for your comment. The EAG notes that interim analyses of successful trials are more likely to detect random high effects than random low effects and, as such, the NOTUS trial is more likely to overestimate, rather than underestimate, treatment effects.

Issue 9 Clarification of SGRQ clinically meaningful threshold value

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG is not clear how the company derived a 3.4 threshold for clinically meaningful SGRQ benefit. "It is not clear how the company's alternative threshold of 3.4 points was reached, and so the 4-point margin appears most appropriate." Page 48	We propose that the sentence be removed.	To clarify, we did not provide an alternative threshold for clinically meaningful benefit. The 3.4 point increment was the dupilumab versus placebo benefit at 52 weeks.	Thank you for highlighting this factual inaccuracy. Reference to the 3.4 point threshold has been removed from the report.

Issue 10 Absolute reduction in trial exacerbation rate per patient per year

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG note that the absolute reduction in exacerbations, dupilumab versus placebo, was small.	We propose that the sentence be modified to: "For instance, while annualised rate of moderate or severe	This modest number should be placed within the context of the clinical trial setting (previously	This is not a factual inaccuracy; no change is required.

We argue that this modest number should be described within the context of the clinical trial setting. "For instance, while annualised rate of moderate or severe exacerbations (the primary outcome) indicated significantly fewer exacerbations with dupilumab, the difference in the number of exacerbations per patient per year was small." Page 65	exacerbations (the primary outcome) indicated significantly fewer exacerbations with dupilumab, the difference in the number of exacerbations per patient per year, ***within the clinical trial setting, was modest***."	provided by the EAG); recognising that exacerbation rates are lower in clinical trials that in the real-world, and potentially lower again due to COVID-pandemic shielding. "The EAG agrees that using data directly from the clinical trials may underestimate the exacerbation rate experienced in clinical practice, and notes that clinical experts stated how COVID-19 may have impacted outcomes during the trial period." (page 77)	

Issue 11 No mortality differential observed in clinical trials, despite high exacerbation event number

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG states that the 'large number of exacerbation events' in the clinical trials might have been expected to result in a mortality differential. However, we believe there are reasons why this is would be an unrealistic expectation in these studies. "However, despite the large number of exacerbations observed across the pooled trials in the one-year treatment period, there was no difference in mortality between treatment arms (1.5% of placebo patients versus 1.6% of dupilumab plus background therapy patients). Page 95	We propose that the sentence be removed	The EAG have recognised that the BOREAS and NOTUS studies were not powered to detect differences in mortality between arms: "While the EAG notes that this approach removes the issue of double counting, the extent to which dupilumab may reduce mortality is uncertain as the study was not powered to detect this" (page 95) Also, we have argued in the economic model that severe exacerbations, in particular, result in a significant and measurable excess mortality. Considering only severe exacerbations, we do not agree that there were a "large number of	This is not a factual inaccuracy; no change is required.

		exacerbations observed across the pooled trials", and therefore do not believe that BOREAS and NOTUS could be expected to report differential mortality.	

Issue 12 Differential in reported percentage of TEAEs associated with dupilumab between BOREAS and NOTUS

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG noted that a lower percentage of TEAEs related to dupilumab were reported in the NOTUS trial compared to BOREAS. We believe these data may be uncertain, as it involves subjective reporting and is inconsistent with the other safety reporting categories. "A lower percentage of TEAEs related to dupilumab were reported in the NOTUS trial (3.2%)	We propose that the sentence be removed	The reporting specifically of TEAEs related to IMP is relatively subjective, because study investigators need to apply "reasonable possibility", and "clinical judgement" assessments to determine a relationship to IMP. This is additionally more difficult to do within the blinded study period. The more objective summary safety reporting indicated overall similar	This is not a factual inaccuracy; no change is required.

than in BOREAS (7.5%), indicating that the pooled analysis may have underestimated the additional TEAEs associated with dupilumab” Page 59		rates of TEAE reporting between placebo and dupilumab, in both BOREAS and NOTUS (participants with any TEAE, severe TEAE, emergent SAE, TEAE leading to death, treatment emergent AESI). Thus, this one subjective differential measure is not consistent with the other measures reported, and therefore it is unreasonable to note this data and ascribe a possible underestimation of additional TEAEs associated with dupilumab in the pooled analysis. The EAG have correctly noted that participants with “any TEAE”, across both placebo and dupilumab arms, were somewhat lower in NOTUS versus BOREAS (page 59). This is consistent with the shorter safety observation	

		period of NOTUS (due to interim analysis).	

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
ID6235 Dupilumab for moderate to severe COPD EAG report – "The disutilities associated with moderate and severe exacerbations derived from the updated analysis were [redacted] and [redacted], respectively." page 100	While we acknowledge that the exacerbation disutilities have been marked as CiC in Table 37 of the EAG report, we request that they also be marked as CiC on page 100 for consistency.	The disutilities associated with moderate and severe exacerbations derived from the updated analysis were [redacted] and [redacted], respectively.	Thank you for highlighting this issue with confidential marking. The mark-up has been amended in the updated report.