Medicinrådet

Bilag til Medicinrådets vurdering af dupilumab til behandling af kronisk obstruktiv lungesygdom

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. dupilumab
2. Amgros' forhandlingsnotat vedr. dupilumab
3. Ansøgning vedr. dupilumab

21. november 2025

Til Medicinrådet,

På vegne af Sanofi A/S, vil jeg takke for muligheden for at give kommentarer til Medicinrådets vurdering af dupilumab til behandling af kronisk obstruktiv lungesygdom. Jeg vil samtidig takke for en god og konstruktiv proces med åben dialog i udarbejdelsen af vurderingen.

Overordnet set oplever vi, at Medicinrådet har lavet en meget velbalanceret vurdering af værdien og omkostningerne ved en positiv anbefaling af dupilumab til behandling af KOL-patienter i Danmark. Vi vil dog fremføre nogle få kommentarer og præciseringer nedenfor, som vi håber, at Medicinrådet vil medtage i sine overvejelser om anbefaling.

I udkast til vurdering nævnes det på side 4, at "Hvis patienter fortsat er i GOLD E efter et år med behandling med LAMA, LABA og ICS kan antibiotika (azithromycin) tillægges. Dupilumab vil kunne anvendes som tillæg til behandlingen efter antibiotika, til patienter, som fortsat er i GOLD E, og som er indenfor indikationen for dupilumab". Vi vil bemærke, at der i de studier, som både markedsføringstilladelsen og ansøgningen til Medicinrådet bygger på og anvender, ikke indgik patienter i behandling med LAMA, LABA, ICS og azithromycin, men patienter i behandling med LAMA, LABA og ICS med type 2 / eosinofil inflammation (eos ≥300). I de opdaterede GOLD guidelines for 2025 præsenteres tre terapimuligheder for den patientgruppe i GOLD E, der behandles med LAMA, LABA og ICS, men som fortsat har eksacerbationer som parallelle, fænotype-baserede valg: Azithromycin til patienter, som er ikke-rygere og har hyppige eksacerbationer; roflumilast, hvis kronisk bronkitis er det dominerende kliniske billede; og dupilumab, hvis der er tydelig type 2 / eosinofil inflammation (eos ≥300) trods tripel behandling. Dansk klinisk praksis bygger på de evidensbaserede guidelines fra GOLD, og det må således antages, at dupilumab ikke vil indgå som en terapimulighed i fremtidig praksis, hvis det forudsættes, at patienterne først skal behandles med azithromycin, som netop ikke anbefales til den patientgruppe, der er relevant for dupilumab. En anbefaling af azithromycin før dupilumab synes at være et ikke-evidensbaseret valg, der kan medføre overforbrug af antibiotika, unødige bivirkninger, uden en opvejende effekt, samt et års forværring af sygdomstilstanden for patienter med en progressiv sygdom.

I udkast til vurdering nævnes det under afsnittet Seponering, side 31; "I dansk klinisk praksis er målet for behandlingen at reducere risikoen for eksacerbationer, fordi eksacerbationer er forbundet med en øget risiko for død. Til patienter med GOLD E bør man stoppe behandlingen, hvis patienten efter et års behandling ikke har en reduktion i den årlige rate af eksacerbationer sammenlignet med det forudgående år". Vi er enige i, at en seponeringsregel kan være en vigtig del af klinisk praksis også under hensyntagen til balancen mellem virkning og bivirkninger. Desuden har en seponeringsregel også økonomiske konsekvenser for omkostningseffektivitet og estimeret fremtidig budgetvirkning. I forbindelse med udarbejdelsen af vores ansøgning vejledte en ekstern klinisk ekspert os til, at den seponeringsregel, der var indarbejdet i den

økonomiske model, som en option man kunne trykke på, blev ændret fra et krav om 50% reduktion i antal eksacerbationer i forhold til året før til en stabilisering i eksacerbationsraten i forhold til året før. Dette blev anført som klinisk mere meningsfuldt under hensyntagen til sygdommens progressive natur, hvor eksacerbationer leder til flere eksacerbationer, hvorfor stabilisering af eksacerbationsraten må tolkes som respons på behandlingen med dupilumab.
I den økonomiske analyse i udkast til vurderingsrapport indgår Medicinrådets seponeringsregel ikke, hvilket må bero på en forglemmelse. Seponeringsreglen bør naturligvis afspejles i Medicinrådets sundhedsøkonomiske analyse for at få et retvisende billede af omkostningseffektiviteten og budgetvirkningen af en positiv anbefaling som grundlag for Rådets anbefaling. Det skal bemærkes, at denne ændring sikrer, at dupilumab er et omkostningseffektivt alternativ under en rimelig antagelse om betalingsvillighed per kvalitetsjusteret leveår på niveau med BNP per capita i Danmark. Budgetvirkningen påvirkes også væsentligt.

I udkast til vurdering anslås, at 1.000 patienter i dag og ca. 200 årligt i fremtiden vil være kandidater til behandling med dupilumab. I Sanofis ansøgning havde vi foretaget et udtræk fra Dansk Register for Kronisk Obstruktiv Lungesygdom (DrKOL). Dette udtræk var begrænset til patienter i GOLD E, med eosinofiltal > 300 mia/l, i behandling på lungeambulatorier med LAMA, LABA og ICS. Udtrækket fandt lignende tal som Medicinrådets. Det skal bemærkes, at udtrækket var flerårigt, og at patientantal var stabile, hvis der tages højde for den stigende prævalens af KOL i Danmark. Henvisningskriterierne fra almen praksis til behandling i lungeambulatorierne har været stabile over tid og inkluderer patientgruppen med GOLD E. Endvidere, måles eosinofiltal i ambulatorierne. Under hensyntagen til Medicinrådets forsigtighedsprincip, bør det anføres, at ovennævnte patientgruppe er begrænset af objektive kriterier. Disse kriterier kan ikke påvirkes af hverken patient eller behandlere. Datagrundlaget hviler på en stabil klinisk henvisningspraksis, hvor patientgruppen under alle omstændigheder historisk har skulle henvises til lungeambulatorie. Medicinrådets seponeringsregel begrænser i tillæg hertil yderligere sandsynligheden for overbehandling, indikationsskred og budgetusikkerhed.

Vi ser frem til, at en stigmatiseret og ofte socialt belastet patientgruppe med 5-årsoverlevelse på niveau med lungecancerpatienter, også får adgang til en ny og effektiv behandlingsmulighed, med løfte om både livsforlængelse og livskvalitetsforbedring som dokumenteret i vurderingen.

Birgitte Fyhn
Head of Public Affairs and Market Access, Danmark

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

Forhandlingsnotat

20.11.2025
KLE/DBS

Dato for behandling i Medicinrådet	17.12.2025
Leverandør	Sanofi
Lægemiddel	Dupixent (dupilumab)
Ansøgt indikation	Dupilumab er indiceret som tillæg til vedligeholdelsesbehandling hos voksne af ukontrolleret kronisk obstruktiv lungesygdom (KOL) karakteriseret ved forhøjet eosinofiltal i blodet, som er i behandling med en kombination af inhalationskortikosteroid (ICS), en langtidsvirkende beta-2-agonist (LABA) og en langtidsvirkende muskarinreceptor-antagonist (LAMA), eller med en kombination af en LABA og en LAMA hvis ICS er uegnet.
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har forhandlet følgende pris på Dupixent (dupilumab):

Tabel 1: Forhandlet pris

Lægemiddel	Styrke (Paknings-størrelse)	AIP (DKK)	Nuværende SAIP, (DKK)	Nuværende rabat ift. AIP	SAIP (DKK) ifm. næste prisregulering	Rabat ift. AIP ifm. næste prisregulering
Dupixent	200 mg, sprøjte (2 stk.)	7.649,96	[redacted]	[redacted]	[redacted]	[redacted]
Dupixent	300 mg, sprøjte (2 stk.)	8.100,58	[redacted]	[redacted]	[redacted]	[redacted]
Dupixent	200 mg, pen	7.649,96	[redacted]	[redacted]	[redacted]	[redacted]

	(2 stk.)					
Dupixent	300 mg, pen (2 stk.)	8.100,58	[redacted]	[redacted]	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling. Det betyder at hvis Medicinrådet ikke anbefaler Dupixent til KOL, indkøbes lægemidlet til nuværende SAIP.

Aftaleforhold

Dupixent indgår i det eksisterende udbud omfattende lægemidlerne til behandling af atopisk eksem, svær astma og svær kronisk rhinosinuitis med næsepolypper.

[redacted]

Konkurrencesituationen

Dupixent blev, som første biologiske behandling, godkendt af EMA, som vedligeholdelsesbehandling hos voksne med ukontrolleret kronisk obstruktiv lungesygdom (KOL). Det forventes at Nucala bliver godkendt af EMA til samme indikationen i starten af 2026 og vurderet i Medicinrådet.

Tabel 1: Lægemiddeludgifter pr. patient pr år.

Lægemiddel	Styrke (pakningsstørrelse)	Dosering*	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandling/år (SAIP, DKK)
Dupixent	300 mg, pen (2 stk.)	300 mg hver anden uge, s.c.	[redacted]	[redacted]

*) Jf. Medicinrådets vurderingsrapport s. 15

Status fra andre lande

Tabel 2: Status fra andre lande

Land	Status	Link
Norge	Under vurdering	Link til information
England	Under vurdering	Link til information
Sverige	Under vurdering	Link til information

Opsummering

[redacted]

[redacted]

Application for the assessment of dupilumab (Dupixent®) for the treatment of chronic obstructive pulmonary disease (COPD)

sanofi

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-code]

Contact information

Contact information	
Name	**Birgitte Fyhn**
Title	Head of Market Access and External Affairs
Phone number	+45 24 88 60 32
E-mail	Birgitte.Fyhn@sanofi.com
Name	**Wiggo Sandberg**
Title	Medical Advisor
Phone number	+47 93 80 49 93
E-mail	Wiggo.Sandberg@sanofi.com
Name	**Line Groth-Pedersen**
Title	Medical Advisor
Phone number	+45 50 46 70 78
E-mail	line.pedersen@sanofi.com

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Tables and Figures

Abbreviations

AE	Adverse event
CEAC	Cost-effectiveness acceptability curves
COPD	Chronic obstructive pulmonary disease
CTCAE	Common Terminology Criteria for Adverse Events
DSA	Deterministic sensitivity analysis
DrKOL	Danish registry for chronic obstructive pulmonary disease
ER	Emergency department
FeNO	Fraction of exhaled nitric oxide
FEV	Forced expiratory volume in the first second
FVC	Forced vital capacity
GP	General practitioner
HRQoL	Health-related quality of life
HSUV	Health state utility value
ICER	Incremental cost-effectiveness ratio
ICS	Inhaled corticosteroid
IRR	Incidence rate ratio
ITT	Intention to treat
LABA	Long-acting beta2-agonist
LAMA	Long-acting muscarinic antagonist
LS	Least square
LY	Life years

MCID	Minimal clinical important difference
MMRM	Mixed model for repeated measures
OR	Odds ratio
PPP	Pharmacy purchasing price
PSA	Probabilistic sensitivity analysis
pre-BD	Pre bronchodilators
SAE	Serious adverse events
SGRQ	St. George's Respiratory Questionnaire
SMR	Standardized mortality ratio
TS	Type 2
QALY	Quality-adjusted life year

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Dupixent®
Generic name	Dupilumab
Therapeutic indication as defined by EMA	Dupixent is indicated in adults as add-on maintenance treatment for uncontrolled chronic obstructive pulmonary disease (COPD) characterised by raised blood eosinophils on a combination of an inhaled corticosteroid (ICS), a long-acting beta2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA), or on a combination of a LABA and a LAMA if ICS is not appropriate.
Marketing authorization holder in Denmark	Sanofi A/S
ATC code	D11AH05
Combination therapy and/or co-medication	Dupilumab can be administered as an add-on to triple therapy with ICS, a LAMA, and a LABA
(Expected) Date of EC approval	July 2024
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No

Overview of the medicine	
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	**From the SmPC** (1)**:** **Atopic dermatitis** • Adults and adolescents: Dupilumab 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: Dupilumab 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: Dupilumab 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 plus another medicinal product for maintenance treatment. • Children 6 years to 11 years of age: Dupilumab 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 fraction of exhaled FeNO who are inadequately controlled with medium- to high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment. **Chronic rhinosinusitis with nasal polyposis (CRSwNP)** • Dupilumab is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe chronic rhinosinusitis with nasal polyposis for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control. **Prurigo Nodularis (PN)** • Dupilumab is indicated for the treatment of adults with moderate-to-severe prurigo nodularis who are candidates for systemic therapy. **Eosinophilic esophagitis (EoE)** • Dupilumab is indicated for the treatment of eosinophilic esophagitis 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.

Overview of the medicine	
Other indications that have been evaluated by the DMC (yes/no)	The DMC has evaluated dupilumab for the following indications: **Atopic dermatitis** • Severe atopic dermatitis in children aged 6 months to five years old who are candidates to systemic therapy. • Severe atopic dermatitis in children aged 6 to 11 years old. • Moderate-to-severe atopic dermatitis in patients aged 12 to 17 years of age. • Moderate-to-severe atopic dermatitis in adult patients. **Asthma** • Children aged 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. • Adults and adolescents (≥12 years) with severe asthma with type 2 inflammation characterised by eosinophilia. • Adults and adolescents (≥12 years) with severe asthma with type 2 inflammation characterised by allergy and concomitant eosinophilia or characterised by allergy and concomitant increased FeNO. **Chronic rhinosinusitis with nasal polyposis** • Add-on therapy with intranasal corticosteroids for the treatment of adults with severe chronic rhinosinusitis with nasal polyposis for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control. **PN** Moderate-to-severe PN who are candidates for systemic therapy
Dispensing group	NBS
Packaging – types, sizes/number of units and concentrations	Dupilumab is available as: • 2 x 200 mg pre-filled syringes • 2 x 200 mg pre-filled pens • 2 x 300 mg pre-filled syringes • 2 x 300 mg pre-filled pen

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Dupilumab is indicated for adults as add-on maintenance treatment for uncontrolled COPD characterized by raised blood eosinophils on a combination of an ICS a LABA, and a LAMA, or on a combination of LABA and LAMA if ICS is not appropriate.
Dosage regiment and administration	Patients with COPD should receive 300 mg dupilumab subcutaneously once every two weeks.
Choice of comparator	The comparator is placebo. In the BOREAS and NOTUS trials, placebo was given as an add-on to triple therapy with LABA/LAMA/ICS, which are currently standard of care in Denmark.
Prognosis with current treatment (comparator)	COPD requires lifelong treatment. Current treatment of COPD includes smoking cessation, inhaled bronchodilators, and rehabilitation (2). The long-acting bronchodilators are more effective than the short-acting and should be administered continuously to prevent or reduce symptoms and prevent exacerbations. However, with the treatment options available today, COPD is still a major cause of morbidity and mortality. COPD patients who have been hospitalised with exacerbations have a high mortality rate during the hospitalisation and a high risk of rehospitalisation (3). In the 2023 annual report from the Danish registry for chronic obstructive pulmonary disease (DrKOL) (4), it is stated that 10,243 patients were admitted to the hospital due to an acute exacerbation in 2023, with a mean admission time of 4.3 days. The readmission rate within 30 days was 16.2% (95% CI: 15.6, 16.8) in 2023 (2,117 out of 13.076 admissions). The proportion of patients who die within the first 30 days of being admitted to the hospital due to an exacerbation was 16.3% in 2023 and the 1-year mortality for patients who are admitted for the first time due to an acute COPD exacerbation was 31.0% in 2022 (4).
Type of evidence for the clinical evaluation	Two head-to-head studies (direct comparative analyses) and a pooled analysis of results from these two studies.
Most important efficacy endpoints (Difference/gain compared to comparator)	BOREAS, intention to treat (ITT): • The annualized rate of moderate or severe exacerbations of COPD at week 52 was 0.78 (95% CI: 0.64, 0.93) in the dupilumab group and 1.10 (95% CI: 0.93, 1.30) in the placebo group, i.e. the relative risk was 0.70 (95% CI: 0.58, 0.86 p <0.001) (5). • The LS mean from baseline in pre-bronchodilator forced expiratory volume in the first second (FEV_1) at week 52 was 153 ml (95% CI: 116, 189) in the dupilumab group and 70 ml (95% CI: 33,

Summary	
	107) in the placebo group with the LS mean difference being 83 ml (95% CI: 38, 128; P<0.001) (5). NOTUS, ITT: • The annualized rate of moderate or severe exacerbations of COPD at week 52 in the dupilumab group was 0.859 (95% CI: 0.699, 1.057) compared to 1.295 (95% CI: 1.048, 1.600) in the placebo group. The relative risk was 0.664 (95% CI: 0.535, 0.823, p = 0.0002) (6). • The LS mean change in pre-bronchodilator FEV1 from baseline to week 52 was +0.115 (SE: 0.021) liter in the dupilumab group compared to +0.054 (SE: 0.020) liter in the placebo group. The LS mean difference was +0.062 liter (95% CI: 0.011, 0.113, p =0.0182) (6).
Most important serious adverse events for the intervention and comparator	The proportion of patients with serious adverse events (SAEs) were generally well balanced between dupilumab and placebo in both trials. In BOREAS, the system organ class with the highest proportion of patients with treatment-emergent SAEs (≥2% in either group) was respiratory, thoracic and mediastinal disorders (dupilumab: 6.4% and placebo: 6.8%), infections and infestations (dupilumab: 4.1% and placebo: 5.5%) and cardiac disorders (dupilumab: 1.9% and placebo: 2.6%). At preferred term level, the most reported treatment-emergent SAE was COPD (i.e., acute exacerbations of COPD; 5.8% in dupilumab and 5.5% in placebo). Per protocol, worsening of COPD was not considered an adverse event (AE) unless it met the seriousness criteria. Pneumonia, COVID-19 and COVID-19 pneumonia were the most frequently reported serious infections. The NOTUS trial reported similar results.
Impact on health-related quality of life	Clinical documentation: In the ITT population, improvement from baseline in the SGRQ total score at week 52 was greater in the dupilumab group than in the placebo group: the LS mean change from baseline at week 52 was −9.945 (SE: 0.636) in the dupilumab group and −6.579 (SE: 0.640) in the placebo group. The LSM difference was −3.366 (95% CI: -4.953, -1.778, <.0001) (5). For EQ-5D-5L, the LS mean change from baseline at week 52 was 0.038 (SE: 0.010) in the dupilumab group and 0.039 (SE: 0.010) in the placebo group. The LSM difference was -0.001 (-0.027, 0.024). Health economic model: The incremental QALY was xxx with dupilumab compared to background therapy.
Type of economic analysis that is submitted	Type of analysis: cost-utility analysis Type of model: Markov model

Summary	
Data sources used to model the clinical effects	Pooled analysis of BOREAS and NOTUS, Whittaker 2022 and Fenwick et al. 2021 (7,8).
Data sources used to model the health-related quality of life	EQ-5D-5L from the NOTUS trial.
Life years gained	xxx years
QALYs gained	xxx QALY
Incremental costs	xxxxxx DKK
ICER (DKK/QALY)	xxxxxx DKK/QALY
Uncertainty associated with the ICER estimate	The results were most sensitive to changes to the mortality adjustment factor that was used to align model mortality with the relevant Danish population and to the patient distributions related the different COPD stages in the model at the end of the amelioration phase.
Number of eligible patients in Denmark	Incidence: xxx Prevalence: xxx
Budget impact (in year 5)	xxxxxxx

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

COPD is a heterogenous and progressive airway disease that is associated with persistent respiratory symptoms, debilitating exacerbations, and inflammation. COPD is characterised by chronic respiratory symptoms such as dyspnoea and cough with or without sputum production, wheezing and chest tightness, and fatigue (9–13). COPD with type 2 (T2) inflammation, or eosinophilic COPD, is an emerging phenotype of COPD with unique clinical characteristics and outcomes (14). Patients with COPD with T2 inflammation experience significant clinical burden characterised by increased mortality,

debilitating symptoms, increased rates of chronic comorbidities, and acute exacerbations of COPD, as well as associated humanistic and economic burden (11,13,15).

Environmental and genetic interactions that damage or alter lung development over the course of a patient's lifetime result in COPD. The primary risk factor associated with the development of COPD is tobacco smoking—and the prevalence of COPD is 5-fold higher for current smokers and nearly 3-fold higher for former smokers vs non-smokers (16). The inhalation of other toxic particles and gases, such as biomass fuel, air pollution, or occupational dust, can also contribute to the development of COPD (17). Although it accounts for few cases, COPD is also associated with a genetic deficiency of α-1-antitrypsin. Further risk factors include the rate of aging, which can be accelerated by reactive oxygen species in tobacco smoke, and impaired lung growth or development, such as for patients who were born prematurely (17).

A COPD diagnosis may be considered based on the presence of risk factors or symptoms, including progressive, persistent dyspnoea that gets worse with exercise; recurrent wheeze; chronic cough that may be intermittent or may be unproductive; and recurrent lower respiratory tract infections. To confirm a COPD diagnosis, spirometry showing the presence of persistent airflow obstruction is required. To determine the presence of airflow obstruction, GOLD recommends post-bronchodilator testing showing the ratio of FEV1 to forced vital capacity (FVC) of <0.7 (17). To determine prognosis and guide therapy, additional assessments determining the severity of disease, symptoms, and a history of exacerbations, must be conducted after diagnosis is confirmed with spirometry.

The severity of COPD is determined by the level of airflow obstruction, assessed based on the post-bronchodilator value of FEV1. GOLD classifies COPD in 4 grades of severity, as presented in Figure 1. In addition to the GOLD classification, as airflow obstruction alone is a poor predictor of a patient's future risk of exacerbations, the GOLD 2023 refined ABE assessment tool was developed. The ABE tool provides information on symptom burden and exacerbation risk in addition to airflow obstruction and classifies patients into 1 of 3 groups: A, B, or E, to guide treatment (see Figure 1). GOLD E patients, i.e. those with ≥2 moderate exacerbations or ≥1 leading to hospital admission, have the worst prognosis.

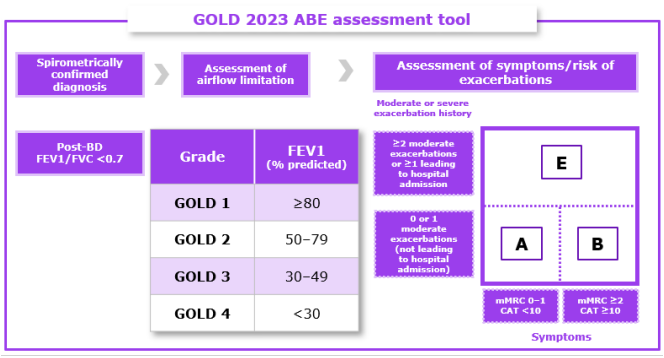


Figure 1: GOLD 2023 ABE assessment tool. Source: GOLD 2023.

3.1.1 The pathophysiology of COPD

An illustration of the pathophysiology and pathology of COPD is presented in Figure 2. COPD arises due to chronic, persistent inflammation in the airways and lungs. Inflammation in COPD is induced by oxidative stress from chronic irritants. The resulting chronic inflammation leads to destructive tissue changes, the development of chronic airflow obstruction, mucus hypersecretion, goblet cell hyperplasia, and loss of ciliary beating on the airway epithelial surface (18). The effects on the airways and lungs can persist long after cessation of smoking or removal of the irritant, with patients continuing to experience airway inflammation (19,20).

The predominant inflammatory pathway is neutrophil-mediated, with neutrophils, macrophages, and CD8+ T lymphocytes playing roles. However, around 10–40% of COPD patients have features of COPD T2 inflammation, or an eosinophilic phenotype (14,21). In eosinophilic COPD, airway epithelial cells release IL-33, a cytokine that attracts immune cells such as T helper cells type 2 (Th2) and type 2 innate lymphoid cells (ILC2). These cell types secrete T2 cytokines (e.g., IL-4, IL-5, IL-13), which results in eosinophil trafficking to tissues and contributes to airway remodelling and parenchymal destruction in COPD (10,22–25). More specifically, IL-13 plays a role in the induction of emphysema, mucus metaplasia, inflammation, and fibrosis, while IL-4 plays a role in the induction of inflammation, cytokine production, and IgE synthesis (22,24–30).

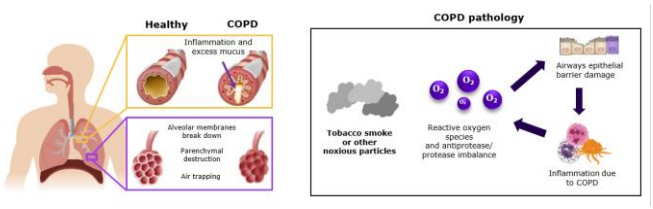


Figure 2: Pathophysiology and pathology of COPD. Source: Barnes 2019 (14).

3.1.2 COPD prognosis and the prognosis with the current treatment options

COPD is a major cause of morbidity and mortality. Globally, COPD is the third leading cause of death, accounting for 6% of total deaths (31). In Denmark, COPD as a single disease is the disease that causes most deaths (4) and the five-year mortality rate after the first exacerbation-related hospitalization is 58.2% (32).

Lung function and COPD exacerbations are predictive of mortality and both moderate and severe exacerbations increase the risk of subsequent exacerbations and death. A large population-based inception cohort study followed patients from their first severe COPD exacerbation to describe the long-term profile of severe COPD exacerbations over time and their association with mortality (33). The cohort of 73,106 patients were followed for 17 years and the median time from the first to the second hospitalized exacerbation was around 5 years and decreased to <4 months from the 9th to the 10th (Figure 3). Mortality after a severe exacerbation peaked to 40 deaths per 10 000 per day in the first week after admission and dropped gradually to 5 after 3 months (33).

This is confirmed by a Denmark-based cohort study of 8,453 COPD patients aged ≥40 years, where patients with a history of 1 moderate exacerbation had an increased risk of subsequent exacerbations and death as compared to those with no exacerbations in a 12-month pre-index period. For patients with one moderate exacerbation during the previous year, the odds ratio (OR) for 1 moderate, ≥2 moderate exacerbations, ≥1 severe exacerbation was 1.58 (95% CI: 1.33, 1.87), 2.60 (95% CI: 2.19, 3.08), 2.08 (95% CI: 1.76, 2.45), respectively. For death, the OR was 1.85 (95% CI: 1.57, 2.17) compared to those with no exacerbations (34). Prevention of exacerbations is therefore a key element in COPD treatment.

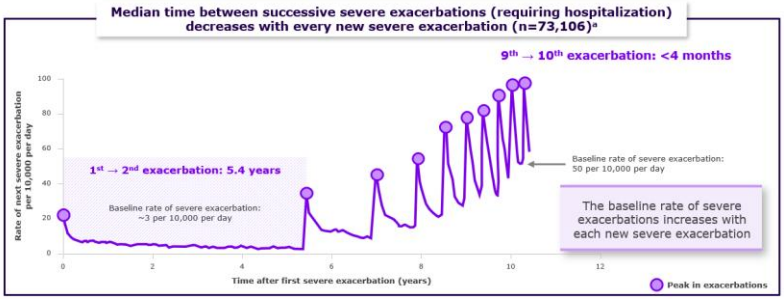


Figure 3: Severe exacerbations increase the risk of subsequent exacerbations. Source: Suissa et al. 2012 (33).

COPD is often the result of cigarette smoking or long-term exposure to other irritants (15). Patients with COPD who smoke experience a higher prevalence of respiratory symptoms and lung function abnormalities, greater decline in lung function, and greater mortality than non-smokers with COPD (5,17,35). Chronic exposure to irritants such as tobacco smoke can cause the release of epithelial-derived cytokines, initiating the T2 inflammatory cascade (36). However, COPD that continues to progress can be found in patients regardless of smoking status.

Given the airway and systemic inflammation associated with COPD, the functioning of extrapulmonary systems may be adversely affected. Consequently, the likelihood of cardiovascular, neurologic, gastrointestinal, and respiratory diseases is increased. Indeed, a Danish study that included 82,964 patients with COPD found that 58% had at least one comorbidity (32). Cardiovascular comorbidities in particular lead to increased mortality. Patients with COPD have an almost fourfold increase in risk of a major cardiovascular event after an exacerbation. The risk of a cardiac event after an exacerbation is highest during the first weeks but remains higher for months after the exacerbation (37,38).

Multimorbidity, or the presence of 2 or more chronic illnesses, affects mortality and hospitalisations independently of the severity of airflow obstruction. Current treatments for COPD often provide only partial disease control, with patients continuing to experience lung function decline, debilitating symptoms and exacerbations.

3.1.3 The influence of COPD on the patients' functioning and health-related quality of life

COPD and its symptoms have detrimental effects on the health-related quality of life (HRQoL). Worse lung function, exacerbations, and persistent respiratory symptoms, including more severe dyspnoea and severity of cough, are associated with worse patient-reported HRQoL and symptoms of anxiety, depression, and sleep disturbance. A global patient survey revealed that the majority of patients with COPD felt that exacerbations prevented them from making plans for the future and impacted daily activities such as walking, sleeping, and speaking (39). Consistent with this, increased daytime sleepiness, decreased total sleep time, decreased sleep efficiency, and levels of fatigue have been reported during an exacerbation (40). Hospitalisation due to a COPD exacerbation has been shown to result in physical and functional impairment in patients, which deteriorates further between discharge from hospital and 1 month following the exacerbation (41). As with their increased clinical burden, patients with COPD with T2 inflammation have a worse HRQoL as compared to those with COPD without T2 inflammation (42).

GOLD recommends multidimensional scales to capture the burden of all COPD symptoms. St. George's Respiratory Questionnaire (SGRQ) is the most widely documented multidimensional scale, but shorter scales like the COPD Assessment Test (CAT™) are more practically applied in a clinical setting (GOLD 2023) (17).

3.2 Patient population

The present application targets patients with moderate to severe COPD with T2 inflammation who has uncontrolled COPD. In the annual report from DrKOL from 2023, it is stated that the prevalence of COPD in Denmark is around 400,000, including mild cases (4). Around 50,000 have severe or very severe COPD with a FEV1 under 50% of the predicted value and around 20,000 hospitalisations per year have COPD as the main diagnosis (3). The number of Danish patients receiving pharmaceutical COPD treatment is around 110,000 to 130,000 patients (4). According to DrKOL, the prevalence of patients treated in an outpatient setting was 14,794, 15,180 and 14,782 in 2021, 2022 and 2023, respectively. The prevalence in 2020 and 2019 was assumed to be equal to 2021 due to missing information from the DrKOL registry in these years. The incidence of patients treated in an outpatient setting is not reported in DrKOL but it is stated how many patients are hospitalized due to an acute exacerbation, which was 10,243 patients in 2023. Of these, 38% was already known in an outpatient setting i.e., 6,329 patients were not previously known in the clinic. According to the clinical expert, this might be used as a proxy for estimating the incidence of COPD patients in an outpatient setting.

Table 1 Incidence and prevalence of COPD in the past 5 years

Year	2019	2020	2021	2022	2023
Incidence in Denmark	6,329	6,329	6,329	6,329	6,329

Year	2019	2020	2021	2022	2023
Prevalence in Denmark	14,794	14,794	14,794	15,180	14,782
Global prevalence *	N/A	N/A	N/A	N/A	N/A

*The global prevalence was not described as the prevalence of COPD in Denmark is high.

It is assumed that patients who meet the criteria for receiving treatment with dupilumab could be patients with moderate to severe COPD with T2 inflammation defined as eosinophil counts over 300 cells/µL who receive triple therapy with LAMA/LABA/ICS therapy, and who have had ≥2 exacerbations demanding treatment with oral corticosteroids or one exacerbation leading to hospitalization in the previous year. According to identified DrKOL data shared with the DMC as part of this application, xxx patients met these criteria in 2021 and will enter the budget impact analysis in year 1 while xxx incident patients will enter in years 2-5.

Table 2 Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	xxxx	xxxx	xxxx	xxxx	xxxx

3.3 Current treatment options

COPD requires lifelong treatment. The goals of COPD treatment are to reduce symptoms, the number and severity of exacerbations, to improve exercise tolerance and health status, improve the HRQoL and to reduce mortality (17). The management of patients with stable COPD is guided based on an assessment of symptoms and history of exacerbations, as defined by GOLD Group. Smoking cessation is the most important intervention for prevention of COPD and reduce COPD progression regardless of GOLD group (3). Additional non-pharmacological interventions include education and self-management, physical activity, and vaccination (e.g., influenza and pneumococcal vaccination) (3).

Pharmacological treatment options for COPD include short-acting bronchodilators e.g., short-acting β2 agonists (SABAs) and short-acting muscarinic antagonists (SAMAs), long-acting bronchodilators e.g., LABAs and LAMAs, ICS, phosphodiesterase-4 (PDE4) inhibitors, macrolide antibiotics, methylxanthines, and mucolytic agents. In Denmark, the long-acting bronchodilators LAMA and LABA are the standard of care (alone or in combination) and might be used in combination with ICS as well (triple therapy). The beneficial effects of triple therapy are most evident in patients with a higher risk of exacerbations and high blood eosinophils (blood eosinophilia of 0.3 mia/L) as patients with increased blood eosinophils have an increased response to ICS (17).

LABA/LAMAs are commonly combined to provide an increased therapeutic effect, including a reduction in exacerbations as compared to monotherapy, while not

increasing the adverse effects of either class. However, LABAs can result in cardiac dysrhythmias, increased risk of myocardial infarction, muscle cramps, hypoglycemia during exercise, hypotension, headaches, and Raynaud phenomenon (43). LAMAs can result in confusion, disorientation, dry mouth, dry skin, sore throat, mydriasis, photophobia, constipation, urinary retention, and gastroesophageal reflux (44). ICS are used in COPD in combination with dual bronchodilators and are shown to reduce the need for rescue therapy, and reduce exacerbation frequency (17). However, ICS is associated with several adverse effects, including an increased risk of pneumonia and oropharyngeal candidiasis (45). ICS may also lead to diabetes or poor diabetes control, cataracts, mycobacterial infection, and fractures (45). As such, the use of ICS should be tailored to individual patient characteristics.

3.4 The intervention

Information on dupilumab can be found in the table below.

Overview of intervention	
Therapeutic indication relevant for the assessment	Dupilumab is indicated for adults as add-on maintenance treatment for uncontrolled COPD characterised by raised blood eosinophils on a combination of an ICS a LABA, and a LAMA, or on a combination of LABA and LAMA if ICS is not appropriate.
Method of administration	Dupilumab is a recombinant human IgG4 monoclonal antibody that inhibits interleukin-4 and interleukin-13 signalling. Dupilumab inhibits IL-4 signalling via the Type I receptor (IL-4Rα/γc), and both IL-4 and IL-13 signalling through the Type II receptor (IL-4Rα/IL-13Rα). IL-4 and IL-13 are major drivers of human type 2 inflammatory disease, such as atopic dermatitis, asthma, CRSwNP, PN, and EoE. Blocking the IL-4/IL-13 pathway with dupilumab in patients decreases many of the mediators of type 2 inflammation (1).
Dosing	Patients with COPD should receive 300 mg subcutaneous dupilumab once every second week.
Dosing in the health economic model (including relative dose intensity)	Patients in the model received 300 mg dupilumab subcutaneously once every second week until progression or toxicity.
Should the medicine be administered with other medicines?	Not necessary.
Treatment duration / criteria for end of treatment	Dupilumab is intended for long-term treatment. The need for continued therapy should be considered at least on an annual basis as determined by physician assessment of the patient's level of disease control.

Overview of intervention	
Necessary monitoring, both during administration and during the treatment period	The need for continued therapy should be considered at least on an annual basis (1). The clinical expert was consulted in terms of the necessary monitoring of COPD patients receiving dupilumab.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	None
Package size(s)	Dupilumab is available as: 2 x 200 mg pre-filled syringes, 2 x 200 mg pre-filled pens, 2 x 300 mg pre-filled syringes, 2 x 300 mg pre-filled pen

3.4.1 The intervention in relation to Danish clinical practice

Biologic treatment is emerging for the treatment of patients with moderate to severe COPD who are uncontrolled on maximally tolerated therapy. Currently, no biologic treatment has been approved for the treatment of COPD. Dupilumab might be used as an add-on treatment to the current standard of care of triple therapy with LABA/LAMA/ICS.

3.5 Choice of comparator(s)

The comparator in the analyses presented in this application is background therapy. In the BOREAS trial and the NOTUS trial, both dupilumab and placebo were administered as an add-on to triple therapy with LABA/LAMA/ICS. In the health economic analysis, triple therapy with fluticasone furoate, vilanterol and umeclidinium (Trelegy Ellipta) was included.

Overview of comparator	
Generic name	Fluticasone furoate, vilanterol and umeclidinium
ATC code	R03AL08

Overview of comparator	
Mechanism of action	Fluticasone furoate/umeclidinium/vilanterol is a combination of ICS/LAMA/LABA. Following oral inhalation, umeclidinium and vilanterol act locally on airways to produce bronchodilation by separate mechanisms and fluticasone furoate reduces inflammation (46). Fluticasone furoate is a corticosteroid with potent anti-inflammatory activity. The precise mechanism through which fluticasone furoate affects COPD symptoms is not known. Corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g. eosinophils, macrophages, lymphocytes) and mediators (e.g. cytokines and chemokines) involved in inflammation (46). Umeclidinium is a long-acting muscarinic receptor antagonist (also referred to as an anticholinergic). Umeclidinium exerts its bronchodilatory activity by competitively inhibiting the binding of acetylcholine with muscarinic receptors on airway smooth muscle. It demonstrates slow reversibility at the human M3 muscarinic receptor subtype in vitro and a long duration of action in vivo when administered directly to the lungs in pre-clinical models (46). Vilanterol is a selective LABA. The pharmacologic effects of 10 beta2-adrenergic agonists, including vilanterol, are at least in part attributable to stimulation of intracellular adenylate cyclase, the enzyme that catalyses the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells (46).
Method of administration	Inhalation
Dosing	The recommended and maximum dose is one inhalation once daily, each day at the same time. Each single inhalation provides a delivered dose (the dose leaving the mouthpiece) of 92 micrograms fluticasone furoate, 65 micrograms umeclidinium bromide equivalent to 55 micrograms umeclidinium and 22 micrograms vilanterol (as trifenatate). This corresponds to a pre-dispensed dose of 100 micrograms fluticasone furoate, 74.2 micrograms umeclidinium bromide equivalent to 62.5 micrograms umeclidinium and 25 micrograms vilanterol (as trifenatate) (46).
Dosing in the health economic model (including relative dose intensity)	One inhalation once daily. No relative dose intensity accounted for.
Should the medicine be administered with other medicines?	No

Overview of comparator	
Treatment duration/ criteria for end of treatment	For as long as the medicine is effective
Need for diagnostics or other tests (i.e. companion diagnostics)	None
Package size(s)	Trelegy Ellipta is available in the following package sizes: • 30 doses of 92+55+22 micrograms powder for inhalation • 90 doses of 92+55+22 micrograms powder for inhalation

3.6 Cost-effectiveness of the comparator(s)

The cost-effectiveness of triple therapy with ICS/LAMA/LABA in COPD has not been assessed.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

In this section, we define the efficacy outcomes considered relevant and necessary to evaluate the effect of dupilumab vs. placebo and describe the rationale for the chosen efficacy outcomes.

Table 3 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Annualised rate of moderate to severe exacerbations **BOREAS** **NOTUS**	Week 52	The number of moderate or severe exacerbation events during the 52-week treatment period was defined as the number of moderate or severe exacerbation events with onset from randomization up to the week 52 visit per patient-year (47). Moderate exacerbations were defined as exacerbations that resulted in treatment with a systemic glucocorticoid, an antibiotic agent, or both. Severe exacerbations were	Both moderate and severe exacerbations were recorded by the investigator in an electronic case report form. The recordings underwent confirmatory adjudication by experts independent of Sponsor for the evaluation. Only the adjudicated-confirmed exacerbations were used for analysis (47). **Missing data**: for patients discontinuing the study intervention before week 52, off-study treatment data up to

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
		defined as exacerbations that led to hospitalization or an emergency medical care visit or that resulted in death (5). For both moderate and severe events to be counted as separate events, they must be separated by at least 14 days. The annualized event rate was the total number of exacerbations that occurred during the treatment period divided by the total number of participant-years treated. Events were adjudicated by independent third party.	week 52 were included in the analysis. For missing data imputation, discontinuing the study follow-up before week 52, analyses were censored at the time of study discontinuation (47).
Change in prebronchodilator FEV_1 from baseline to week 52 **BOREAS** **NOTUS**	Week 52	The FEV_1 was the volume of air exhaled from the lungs in the first second of a forced expiration as measured by spirometer. Spirometry was performed after a wash out period of bronchodilators according to their action duration.	The outcome was analysed using MMRM with the change from baseline in corresponding endpoint values up to corresponding weeks as response variables, and factors for treatment group, age, sex, height (age, sex and height are only included for spirometry endpoint analyses), region (pooled country), ICS dose at baseline, smoking status at screening, visit, treatment-by-visit interaction, baseline value of the endpoint, and baseline-by-visit interaction as covariates. **Missing data:** For patients discontinuing the study intervention prior to week 12 or week 52, all data collected after discontinuation were used in the analysis. For missing data imputation, missing data were imputed latently by MMRM based on missing at random assumption (47).

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Change in SGRQ total score from baseline **BOREAS** **NOTUS**	Week 52	The SGRQ is a 50-item self-administered questionnaire designed to measure and quantify the health status/HRQoL of adult patients with airflow limitations. Scores by dimension are calculated for 3 domains: symptoms, activity, and impacts (psycho-social), as well as a total/global score that ranges from 0-100. Lower scores indicate better health status/HRQoL.	The outcome was analysed using MMRM with the change from baseline in corresponding endpoint values up to corresponding weeks as response variables, and factors for treatment group, age, sex, height (age, sex and height are only included for spirometry endpoint analyses), region (pooled country), ICS dose at baseline, smoking status at screening, visit, treatment-by-visit interaction, baseline value of the endpoint, and baseline-by-visit interaction as covariates. **Missing data:** For patients discontinuing of the study intervention prior to week 12 or week 52, all data collected after discontinuation were used in the analysis. For missing data imputation, missing data were imputed latently by MMRM based on missing at random assumption (47).
SGRQ total score improvement ≥4 points **BOREAS** **NOTUS**	Week 52	A responder was defined as a patient with improvement from baseline in SGRQ total score at week 52 by ≥4 points. Patients with improvement <4 points or with missing values were considered as non-responders. The percentage of patients who achieved a clinically meaningful response in SGRQ total score (reduction [improvement] by ≥4 points)/responders were reported.	The outcome was analysed using a logistic regression model with treatment group, region (pooled country), ICS dose at baseline, smoking status at screening, and baseline SGRQ total score as covariates. **Missing data:** For patients discontinuing of the study intervention prior to week 52, off-study intervention data were included in the analysis (treatment policy strategy). For missing data imputation, participants having missing data at week 52 were considered as non-responders (47).

* Time point for data collection used in analysis (follow up time for time-to-event measures)

Validity of outcomes

Annualized rate of moderate to severe exacerbations

According to Jones et al. 2014 (48), reduction in frequency of 20% has been suggested as a reasonable MCID for exacerbations, however, the development of an MCID for exacerbations is complicated by the lack of a uniform definition for exacerbations and severity grading as well as underreporting. Moreover, the distribution of exacerbation rates is skewed, with seasonal variation and substantial inter- and intra-patient variability in frequency. Thus, there is presently no validated MCID for exacerbations.

Change in prebronchodilator FEV1 from baseline to week

Improving lung function is an endpoint frequently used by regulatory authorities in interpreting drug efficacy in COPD trials (48). However, opinions on what constitutes an MCID for FEV_1 vary and no validated MCID exists for lung function in COPD. The American Thoracic Society/European Respiratory Society taskforce has defined a range of 100 to 140 ml (48). Regulators consider a change of 5 to 10% from baseline as clinically important and a change of less than 3% from baseline as not clinically important (48). An MCID of 100 ml for pre-dose or trough FEV_1 has been proposed, based on clinical anchoring of endpoints such as exacerbations, perception of dyspnea, and decline in lung function, but not survival.

St. George's Respiratory Questionnaire

The St. George's Respiratory Questionnaire (SGRQ) is a validated 50-item questionnaire designed to measure and quantify health status in adult patients with chronic airflow limitations. It has been recognized as a clinically important patient reported outcome assessment tool providing supportive evidence of efficacy in clinical trials and used in a range of respiratory diseases including COPD. GOLD recommends multidimensional scales to capture the burden of all COPD symptoms and the SGRQ is the most widely documented multidimensional scale. A MCID of 4 units for the SGRQ in COPD has been reported in Jones 2005 (49).

4. Health economic analysis

The health economic analysis in the present application is a cost-utility analysis assessing the incremental cost per quality-adjusted life year (QALY) of treating patients with moderate to severe COPD with type-2 inflammation with dupilumab compared to treatment with background therapy. The health economic model was informed by the pooled analysis of dupilumab and background therapy from BOREAS and NOTUS, due to the similarities of these two trials. In both arms in the model, patients received background therapy which consisted of triple therapy with LABA/LAMA/ICS in accordance with the trials and Danish clinical practice. In the following, we present the health economic model applied in the analysis.

4.1 Model structure

A cohort Markov model structure with a decision tree component in the first year (trial period) was developed. To represent the natural history of the COPD patient over time, the model captured the effect of two parameters:

- **FEV_1 percent of predicted:** FEV_1% of the patient divided by the average FEV_1% in the population for any person of similar age, sex, and body composition. FEV_1 decline was considered a surrogate for the natural decline of the disease and in the clinic, therapies are analysed on its FEV_1 impact over time.
- **Exacerbation:** Exacerbation events are characterised by acute worsening of symptoms. There is evidence supporting the effect of exacerbation on mortality (7,50), FEV_1 decline (8,51), and future exacerbation events (7).

Thus, a model structure was developed 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. The full model structure is presented in Figure 4.

4.1.1 Decision tree component of the model

An upfront decision tree was applied to replicate the first 52 weeks (trial period) that splits patients into health states based on the COPD severity level. At baseline (week 0), patients were split across the four COPD severity stages: mild, moderate, severe, and very severe COPD. In addition, patients were split based on their exacerbation status: no exacerbation, recent moderate exacerbation, and recent severe exacerbation at the end of 52 weeks.

The decision tree part of the model was originally developed to enable modeling of the effect of amelioration of FEV1 levels upon receiving treatment during the trial period as observed in the trials. The amelioration of FEV1 levels can be disabled by the user and the Danish base case had this enabled.

The decision tree calculated the state occupancy at week 2 (amelioration phase) based on the treatment-specific probabilities, separately for dupilumab + background therapy and background therapy and similarly, the state occupancy at week 52 (maintenance phase).

The key rationale for including the decision tree component was that patients experience amelioration of FEV_1 levels upon receiving treatment during the trial period. As shown in Figure 9, where the FEV_1 level trajectory of patients in the BOREAS trial is shown, FEV_1 levels improve from baseline and in the first 2 weeks after treatment. In addition, the FEV_1 levels are maintained from week 2 to the end of the trial period. Thus, the decision tree component in Figure 4 was split into an amelioration phase and maintenance phase where the state occupancy (across severity of GOLD stages) at the end of 2 weeks and the end of 52 weeks was calculated. Beyond 52 weeks (the observed trial period), the Markov component of the model took over and it did not account for transitions associated with amelioration i.e., patients' COPD severity could only deteriorate over time, and the distribution of patients across health states at the start of the Markov model were derived via the decision tree at week 52.

Based on the life-years (LYs) accrued by patients across the four COPD severity stages and the exacerbation rate stratified by the COPD stages, the number of exacerbations experienced by patients in the trial period (stratified by moderate exacerbation and severe exacerbation), and proportion of patients who experience ≥1 moderate exacerbation (no severe exacerbation) and ≥1 severe exacerbation was calculated. Since patients can experience more than one exacerbation in the trial period, the proportion of patients who had 1, 2, and 3+ exacerbations (from the trials) was used to stratify the patients further, please see Table 4.

Table 4 Exacerbation stratification in the decision tree (trial period) at week 52

Recent exacerbation status[a]	Notes
No exacerbation	Calculated as the total number of patients should sum to 1.
≥1 moderate exacerbation[b]	Derived based on the moderate exacerbation rate (no severe) from the selected trial and population.
1 moderate only	The proportion of patients who had 1 moderate, 2 moderate, and 3+ moderate exacerbations in the trial period was 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 population.
1 severe	Similar approach as moderate exacerbation.
2 severe	
3+ severe	

[a]The proportion of patients in the no exacerbation, ≥1 moderate exacerbation, and ≥1 severe exacerbation states were calculated for each COPD severity stage. It was also calculated separately for dupilumab + background therapy and background therapy arms. Patients on dupilumab + background therapy was split further into responders and non-responders at week 52. [b]The exacerbation rate was split into a moderate only exacerbation rate (no severe) 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.

4.1.1.1 Distribution of patients based on the number of exacerbations

The distribution of patients based on the number of exacerbations was a key input in the model as it determines the state occupancy at the start of the Markov model for each arm. It was derived separately for dupilumab + background therapy and background therapy. The distribution of patients by the number of exacerbations derived from the trial period was assumed to be constant throughout the model horizon, due to lack of data beyond the trial period. Hence, the distribution of patients stratified by the number of exacerbations were derived separately for responders and non-responders to dupilumab treatment, please see Table 5. Non-responders to dupilumab treatment were assumed to have the distribution of background therapy.

Table 5 Distribution of patients based on 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])			
≥1 moderate exacerbation	Derived via moderate and severe exacerbation rate (all patients[a])			
1 moderate	Proportion of patients in 1, 2, and 3+ moderate exacerbations are derived separately for responders and all patients.			
2 moderate				
3+ moderate				
≥1 severe exacerbation	Derived via moderate and severe exacerbation rate (all patients)			
1 severe	Proportion of patients in 1, 2, and 3+ severe exacerbations are derived separately for responders and all patients[b].			
2 severe				
3+ severe				

[a] Exacerbation rates for all patients are used for the trial period as the response assessment occurs at the end of 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. This distinction is necessary only for dupilumab treatment where there is a response assessment. For patients receiving background therapy, there was no such distinction as patients do not discontinue background therapy due to response assessment.

4.1.2 Markov component of the model

The COPD severity states (mild, moderate, severe, and very severe COPD) along with the recent exacerbation status (no exacerbation, 1 moderate exacerbation, 2 moderate exacerbation, 3+ exacerbations) were used as health states in the Markov model. Mild COPD was included in the Markov model as some patients experienced amelioration of GOLD stages in the trial period of BOREAS and NOTUS. There were seven states based on patients' recent exacerbation status within each COPD severity state, resulting in a 28-state Markov model with a self-absorbing death state. Patients could only experience a decline of their COPD severity over lifetime; hence, no transitions associated with amelioration was permitted.

The starting health state occupancy at the beginning of the Markov model was derived from the decision tree for both arms. The Markov model had a cycle length of 1 year and ran for a lifetime horizon (capped when the cohort reached 100 years) in the base case. The model is flexible to consider other user-defined horizons. Transitions in the Markov model is further described in section 8.

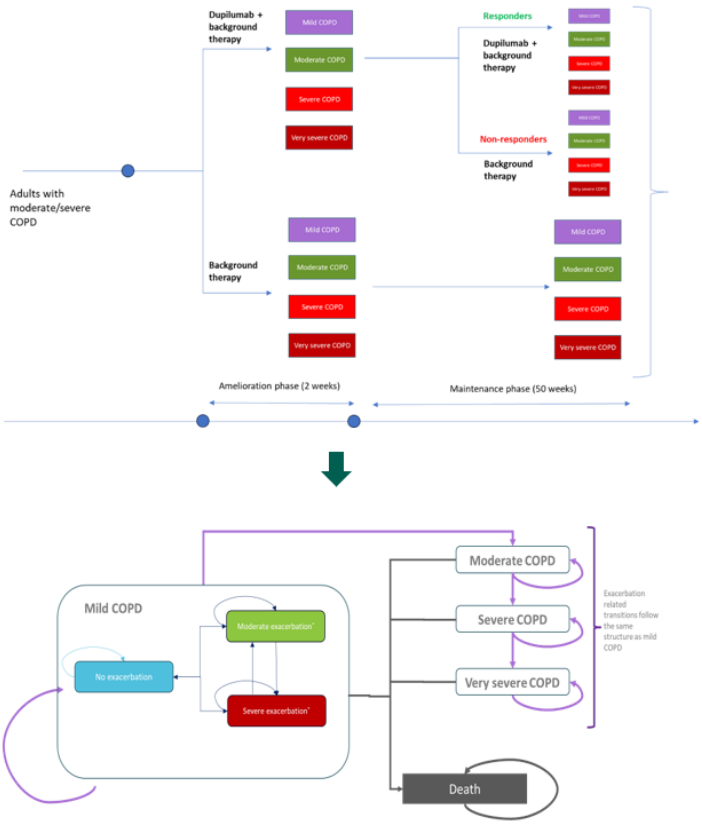


Figure 4: Full model structure with the decision tree component and Markov component

Abbreviation: COPD: chronic obstructive pulmonary disease. *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. Thus, each of the four COPD severity states has 7 sub states resulting in 28 states in total.

At any given cycle, patients could experience two types of transition:

- Transitions within a COPD stage: transitions associated with exacerbation
- Transitions across COPD stages: transitions associated with FEV_1 change (e.g., mild COPD to moderate COPD)

At any given cycle, patients were in one of the seven exacerbation-associated states within a COPD stage, and they could experience one of the following events: ≥1 moderate exacerbation (no severe exacerbation), ≥1 severe exacerbation, and no exacerbation. Because the cycle length was 1 year, patients could experience multiple exacerbation events; therefore, they were further divided into 1, 2, and 3+ exacerbations as shown in Table 6.

Table 6 Transitions within COPD state based on exacerbations

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 (no severe) 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				

[a]Moderate exacerbation was further divided into 1, 2, and 3+ moderate exacerbations based on the trial-based distribution of patients in Table 5. The same approach was followed for severe exacerbation. The transition probabilities of within COPD stage transition were derived separately for each COPD stage.

For transitions across COPD stages, the model has the flexibility to consider a treatment effect period, where it was assumed that the patients' transition across COPD stages was derived from the trial, thus, the treatment effect of dupilumab and background therapy observed in the trial period where patients' FEV_1 levels remained stable in the maintenance period (week 2 to week 52) was assumed to hold in the treatment effect period. Beyond the treatment effect period, patients experienced a natural decline of FEV_1 and thus transitioned across COPD stages over time. The model assumed that patients would experience the exacerbation probabilities associated with the destination COPD state: for example, if a patient with mild COPD and 1 recent severe exacerbation switched to moderate COPD, then the patient experienced the exacerbation probabilities associated with moderate COPD and 1 recent severe exacerbation in a given cycle. Please see section 8 for how transition probabilities were derived.

4.1.2.1.1 Mortality in the model

In addition to transitions within a COPD stage and transitions across COPD stages, patients could experience death events and transition to the self-absorbing death state and were subtracted from the model trace at each cycle. Patients' mortality was derived from the elevated mortality stratified by COPD stages and their recent exacerbation status. Mortality is further described in section 8.

4.2 Model features

The health economic analysis had a limited societal perspective in accordance with the DMC method guideline and the time horizon in the analysis was lifetime, which was defined as the years until the patients reached 100 years of age. This time horizon was considered long enough to capture the long-term clinical and economic impacts of COPD, a chronic disease requiring treatment until end of life, while limiting uncertainty inherent in projecting health outcomes beyond trial periods. Costs and health-related outcomes were discounted at a rate of 3.5% (52). Table 7 presents a summary of the model features.

Table 7 Features of the economic model

Model features	Description	Justification
Patient population	Moderate to severe COPD with type-2 inflammation	Based on EMA indication and trial population. The patient starting age in the model was set to 72 years (cf. section 8.1.4.2).
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Lifetime (until patients reach 100 years)	To capture the long-term clinical and economic impacts of COPD, a chronic disease requiring treatment until end of life, while limiting uncertainty inherent in projecting health outcomes beyond trial periods.
Cycle length	1 year	Consistent with assessment of treatment response in clinical practice.
Half-cycle correction	Yes	To estimate the costs more accurately across the model cycles.
Discount rate	3.5% for years 0-35 of the model's time horizon 2.5% for years 36-70 of the model's time horizon 1.5% for years 71+ of the model's time horizon	The DMC applies a discount rate of 3.5% for the first 35 years, 2.5% for years 36-70 and 1.5% for all years beyond 70 of the model's time horizon based on the discount rate presented by the Ministry of Finance (52).
Intervention	Dupilumab as an add-on to triple therapy with ICS/LAMA/LABA	N/A
Comparator(s)	Background therapy with ICS/LAMA/LABA	ICS/LAMA/LABA is standard of care in Denmark for moderate to severe COPD with type-2 inflammation

Model features	Description	Justification
Outcomes	FEV_1, exacerbations, mortality, HRQoL and safety	To represent the natural history of the COPD patient over time. FEV_1 decline is considered a surrogate for the natural decline of the disease and pharmacotherapies are analysed on its FEV_1 impact over time. Exacerbations may have an impact on mortality, CV events and FEV_1 decline and therefore included in the model.

The health economic model is Excel-based. The deterministic results are updated automatically if any input values or parameters are changed. To obtain updated deterministic sensitivity analysis (DSA) results and probabilistic sensitivity analysis (PSA) results, the user must click on the "Run DSA" button and the "Run PSA" button, respectively.

The model has two "Markov Engines" (i.e., the 'Markov_Engine_1' and 'Markov_Engine_2' sheets).

5. Overview of literature

The clinical assessment in the present application was based on the two placebo-controlled studies the BOREAS trial and the NOTUS trial. Therefore, a literature search for efficacy and safety evidence was not conducted.

5.1 Literature used for the assessment of health-related quality of life

N/A as the assessment of HRQoL was based on the BOREAS and NOTUS studies.

Table 8 Relevant literature included for (documentation of) health-related quality of life (See section 10), N/A

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
N/A		

5.2 Literature used for inputs for the health economic model

N/A as the inputs for the health economic model were based on the BOREAS and NOTUS studies.

Table 9 Relevant literature used for input to the health economic model, N/A

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
N/A			

6. Efficacy

6.1 Efficacy of dupilumab compared to placebo for patients with moderate to severe COPD with type-2 inflammation

6.1.1 Relevant studies

The efficacy and safety of dupilumab in patients with moderate to severe COPD with type-2 inflammation has been assessed in two almost identical trials: the BOREAS and NOTUS trials. Both trials were multinational, randomised, double-blind, placebo-controlled, parallel-group, 52-weeks, pivotal phase 3 trials that studied the efficacy and safety of dupilumab in patients with uncontrolled COPD (i.e., ≥2 moderate or ≥1 severe exacerbations in the previous year and MRC ≥2), moderate-to-severe airflow obstruction (i.e., post-BD FEV1 >30% to ≤70% of predicted), and evidence of type-2 inflammation, on top of established background therapy of LAMA/LABA/ICS (unless ICS was contraindicated). In addition, patients had an eosinophil count of ≥300/µL, and an elevated risk of exacerbations despite prior treatment with standard triple therapy. BOREAS included patients aged 40–80 years, while NOTUS included patients aged 40–85 years. As the two studies are head-to-head studies of dupilumab and placebo, no additional studies were used in the comparison. Table 10 presents an overview of the two studies and Figure 5 presents the study designs.

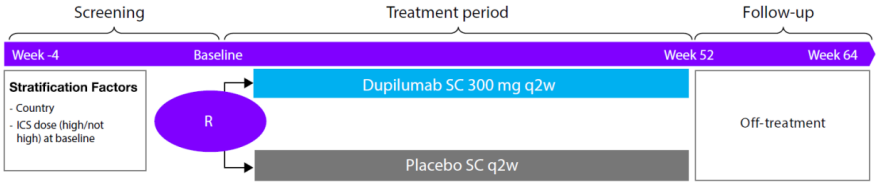


Figure 5: Study design of BOREAS and NOTUS

Figure note: In the NOTUS trial, an additional stratification factor was smoking status. Background therapy: triple therapy (ICS/LABA/LAMA) for 3 months and stable dose ≥1; LABA+LAMA allowed if ICS contraindicated.

The BOREAS and NOTUS trials consisted of 3 periods: a screening period of 4 weeks ± 1 week, a treatment period of 52 weeks ± 3 days, and a post-treatment period of 12 weeks ± 5 days that examined safety outcomes and where patients continued their background LABA/LAMA/ICS therapy. 2,599 patients were screened for eligibility In BOREAS and 939 patients were randomised; 468 were randomised to dupilumab and 471 were randomised to placebo and comprised the ITT population. The disposition of patients in the BORAS trial is presented in Figure 6.

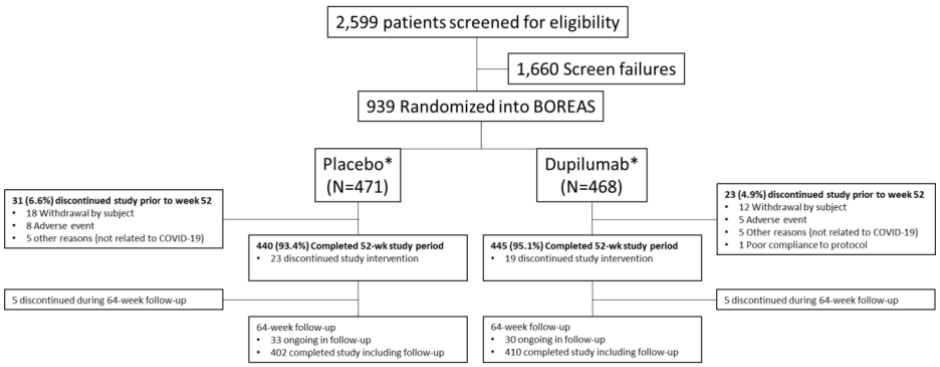


Figure 6: Patient disposition in the BOREAS trial. Source: supplementary material for Bhatt et al. 2023.

Figure note: The study period was the study intervention period + post-intervention follow-up period. *One participant who was allocated to the placebo group inadvertently received a single dose of dupilumab on day 40 and was included in the dupilumab group for the safety analysis.

2,769 patients were screened for eligibility in NOTUS, and 935 were randomised; 470 were randomised to dupilumab and 465 to placebo and comprised the ITT population. The disposition of patients in the NOTUS trial is presented in Table 67.

Table 10 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
BOREAS, NCT03930732 (Bhatt et al. 2023 (5))	Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group study	Treatment period of 52 weeks (±3 days) treatment period. Hereafter, patients entered a 12-week (±5 days) follow-up safety period (64 weeks in total), where the patients no longer received dupilumab or placebo	Patients aged 40-80 with uncontrolled COPD (i.e., ≥2 moderate or ≥1 severe exacerbations in the previous year and MRC ≥2), moderate-to-severe airflow obstruction (i.e., post-BD FEV1 >30% to ≤70% of predicted), and evidence of type-2 inflammation, on top of established background therapy of LAMA/LABA/ICS (unless ICS was contraindicated). Patients were either current or former smokers with a smoking	Subcutaneous dupilumab as add-on therapy at a dose of 300 mg once every 2 weeks for 52 weeks	Placebo to match the intervention	Primary endpoint: • The primary endpoint was the annualized rate of moderate or severe COPD exacerbations over the 52-week treatment period Secondary endpoints: • Change in pre-bronchodilator (pre-BD) FEV1 from baseline to week 12 • Change in pre-BD FEV1 from baseline to week 52 • Change from baseline to week 52 in the SGRQ total score • Proportion of patients with SGRQ score improvement from baseline ≥4 points at week 52 • Change in pre-BD FEV1 from baseline through weeks other than 12 and 52 (i.e., weeks 2, 4, 8, 24, 36, and 44) • Change in post-BD FEV1 from baseline to weeks 2, 4, 8, 12, 24, 36 and 52 • Change in forced expiratory flow (FEF) 25-75% from baseline to weeks 2, 4, 8, 12, 24, 36, 44, and 52 • Annualized rate of severe COPD exacerbations compared to placebo over the 52-week treatment period • Time-to-first moderate or severe COPD exacerbation compared with placebo during the 52-week treatment period Endpoints in the pre-specified FENO ≥20 ppb subgroups:

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
			history of at least 10 pack-years an no history of or current diagnosis of asthma.			• Change in pre-BD FEV1 from baseline to week 12 • Change in pre-BD FEV1 from baseline to week 52 • Annualized rate of moderate or severe COPD exacerbation compared to placebo over the 52-week treatment period.
NOTUS, NCT04456673 (clinical study report)	Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group study	Treatment period of 52 weeks (±3 days) treatment period. Hereafter, patients entered a 12-week (±5 days) follow-up safety period (64 weeks in total), where the patients no longer received dupilumab or placebo	Patients aged 40-85 with uncontrolled COPD (i.e., ≥2 moderate or ≥1 severe exacerbations in the previous year and MRC ≥2), moderate-to-severe airflow obstruction (i.e., post-BD FEV1 >30% to ≤70% of predicted), and evidence of type-2 inflammation, on top of established background therapy of LAMA/LABA/ICS (unless ICS was contraindicated).	Subcutaneous dupilumab as add-on therapy at a dose of 300 mg once every 2 weeks for 52 weeks	Placebo to match the intervention	Primary endpoint: • The primary endpoint was the annualized rate of moderate or severe COPD exacerbations over the 52-week treatment period Secondary endpoints: • Change in pre-BD FEV1 from baseline to week 12 • Change in pre-BD FEV1 from baseline to week 52 • Change from baseline to week 52 in the SGRQ total score • Proportion of patients with SGRQ score improvement from baseline ≥4 points at week 52 • Change in pre-BD FEV1 from baseline through weeks other than 12 and 52 (i.e., weeks 2, 4, 8, 24, 36, and 44) • Change in post-BD FEV1 from baseline to weeks 2, 4, 8, 12, 24, 36 and 52 • Change in forced expiratory flow (FEF) 25-75% from baseline to weeks 2, 4, 8, 12, 24, 36, 44, and 52 • Annualized rate of severe COPD exacerbations compared to placebo over the 52-week treatment period

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
			Patients were either current or former smokers with a smoking history of at least 10 pack-years an no history of or current diagnosis of asthma.			• Time-to-first moderate or severe COPD exacerbation compared with placebo during the 52-week treatment period

6.1.2 Comparability of studies

N/A due to head-to-head studies.

6.1.2.1 Comparability of patients across studies

Table 11 presents the baseline characteristics of patients in the BOREAS and NOTUS studies as well as the characteristics of the patients in the pooled analysis.

Table 11 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	BOREAS		NOTUS		Pooled analysis	
	Placebo (n=471)	Dupilumab (n=468)	Placebo (n=465)	Dupilumab (n=470)	Placebo (n=936)	Dupilumab (n=938)
Age, mean (SD)	65.2 (8.1)	65.0 (8.0)	64.9 (8.5)	65.2 (8.1)	65.0 (8.3)	65.1 (8.0)
Males, n (%)	322 (68.4)	298 (63.7)	312 (67.1)	320 (68.1)	634 (67.7)	618 (65.9)
Race, n (%)						
White	397 (84.3)	393 (84.0)	416 (89.5)	422 (89.8)	813 (86.9)	815 (86.9)
Black/of African descent	2 (0.4)	3 (0.6)	8 (1.7)	4 (0.9)	10 (1.1)	7 (0.7)
Asian	67 (14.2)	67 (14.3)	3 (0.6)	7 (1.5)	70 (7.5)	74 (7.9)
American Indian or Alaska	4 (0.8)	3 (0.6)	26 (5.6)	22 (4.7)	30 (3.2)	25 (2.7)
Native Hawaiian or other	1 (0.2)	0	0	1 (0.2)	1 (0.1)	1 (0.1)
Multiple	0	2 (0.4)	8 (1.7)	12 (2.6)	8 (0.9)	14 (1.5)
Unknown	0	0	0	0	0	0
Not reported	0	0	4 (0.9)	2 (0.4)	4 (0.4)	2 (0.2)
Weight in kg, mean (SD)	77.51 (17.60)	76.51 (17.25)	78.74 (18.29)	79.74 (17.11)	78.12 (17.95)	78.13 (17.24)
BMI (kg/m2), mean (SD)	27.65 (5.73)	27.51 (5.44)	27.78 (5.56)	28.09 (5.29)	27.71 (5.64)	27.80 (5.37)
Baseline blood eosinophil (giga/L), mean (SD)	0.41 (0.33)	0.39 (0.26)	0.40 (0.31)	0.41 (0.36)	0.40 (0.32)	0.40 (0.31)

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

The consulted clinical expert has provided Sanofi with register data to assess the characteristics of the relevant Danish patient population with eosinophil count of ≥300/µL who receive triple therapy, and who have had ≥2 moderate exacerbations or one severe exacerbation in the previous year, please see Table 12.

The health economic model is based on the inclusion criteria of the BOREAS and NOTUS trials (pooled analysis). Specifically, the model focuses on moderate to severe COPD patients with a blood eosinophil count of at least 300/µL. The base case considered the ITT population from the pooled analysis of BOREAS and NOTUS.

Table 12 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (DrKOL 2021, data on file)	ITT population in pooled analysis of BOREAS and NOTUS	Value used in health economic model
Age	Average: XXX	Mean age: 65.1 (SD: 8.2)	66.6
Age groups	30-39 years: XXX	Not reported	Not included
	40-49 years: XXX	40-64: 42.8%	
	50-59 years: XXX		
	60-69 years: XXX		
	70-79 years: XXX	65-74: 44.2% 75-80: 12.5%	
	80-89 years: XXX	81-85: 0.5%	
	≥90 years: XXX	Not reported	
Gender	Female: XXX Male: XXX	Female: 33.2% Male: 66.8%	Male: 46.3%
BMI			
BMI categories	Underweight (10-19): XXX	<25: 33.7% ≥25-<30: 36.5%	Not included
	Normal weight (20-24): XXX		
	Overweight (25-29): XXX		

	Obesity (30-50): XXX	≥30-<35: 19.2%	
	NA: XXX	≥35: 10.6%	
Smoking status			
Current smoker	XXX	30% (BOREAS)	Not included
Former smoker	XXX	70% (BOREAS)	
Never smoked	XXX	Not included	
NA	XXX	Not reported	
MRC grade			
Grade 1	XXX	Not reported	Not included
Grade 2	XXX		
Grade 3	XXX		
Grade 4	XXX		
Grade 5	XXX		
Exacerbations the last year			
0 the last year	XXX	Not reported	Not included
1 the last year	XXX	Not reported	
2 or more the last year	XXX	Mean: 2.3 ± 1.0 (BOREAS)	
Baseline blood eosinophil count	Mean (SD): XXX	Pooled: mean 0.40 giga/L (SD: 0.32)	Not included

6.1.4 Efficacy – results per the BOREAS study

Efficacy results from the ITT population are presented in this section. Improvements in the SGRQ score are presented in section 10.

6.1.4.1 Annualized rate of moderate or severe COPD exacerbations

In the BOREAS trial, dupilumab led to a statistically significant and clinically meaningful reduction in the annualized rate of moderate or severe COPD exacerbations during the 52-week trial period. The annualized rate of moderate or severe exacerbations of COPD at week 52 was 0.78 (95% CI: 0.64, 0.93) in the dupilumab group and 1.10 (95% CI: 0.93, 1.30) in the placebo group, i.e. the relative risk was 0.70 (95% CI: 0.58, 0.86 p <0.001) (5).

Figure 7 presents the cumulative mean number of moderate or severe exacerbations during the 52-week trial period in each group and Figure 8 presents the time to the first moderate or severe exacerbation.

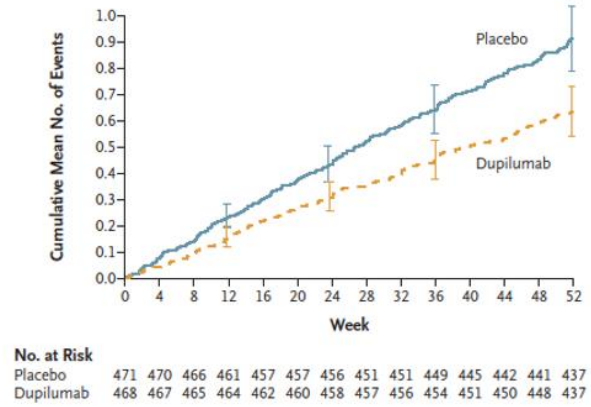


Figure 7: the cumulative mean number of moderate or severe exacerbations in the BOREAS trial. Source: Bhatt et al. 2023.

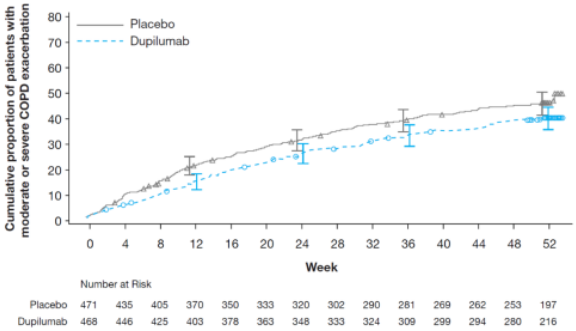


Figure 8: time to first moderate to severe COPD exacerbation in the BOREAS trial ITT population. Source: supplementary material in Bhatt et al. 2023.

6.1.4.2 Change in pre-bronchodilator FEV1 from baseline to week 12 and 52

At baseline, the mean in pre-bronchodilator FEV1 was 1.28 (SD: 0.45, 95% CI: 1.24, 1.32) in the dupilumab group and 1.32 (SD: 0.46, 95% CI: 1.28, 1.36) in the placebo group. At week 12, the mean 1.44 (SD: 0.55, 95% CI: 1.29, 1.39) in the dupilumab group and 1.38 (SD: 0.51, 95% CI: 1.33, 1.43) in the placebo group. The LS mean change from baseline in the pre-bronchodilator FEV_1 at week 12 was 160 ml (95% CI: 126, 195) in the dupilumab group and 77 ml (95% CI: 42, 112) in the placebo group with the LS mean difference being 83 ml (95% CI: 42, 125; P<0.001) at week 12. This improvement was observed within 2 weeks after the initiation of dupilumab or placebo and was sustained through week 52, where the LS mean from baseline in pre-bronchodilator FEV_1 was 153 ml (95% CI: 116, 189) in the dupilumab group and 70 ml (95% CI: 33, 107) in the placebo group with the LS mean difference being 83 ml (95% CI: 38, 128; P<0.001) (5). The mean in pre-

bronchodilator FEV1 at week 52 was 1.44 (SD: 0.57, 95% CI: 1.39, 1.49) in the dupilumab group and 1.39 (SD: 0.53, 95% CI: 1.34, 1.44) in the placebo group. The LS mean change from baseline in pre-bronchodilator FEV_1 from the ITT population is presented in Figure 9.

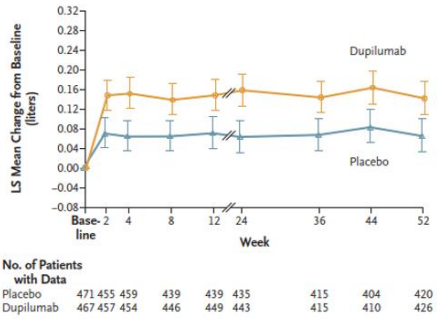


Figure 9: LS mean change from baseline in pre-bronchodilator FEV_1 at week 12 up to week 52 in the BOREAS trial. Source: Bhatt et al. 2023.

Table 13 presents results from the comparative analyses on dupilumab and placebo from the BOREAS trial.

Table 13 Results from the comparative analysis of dupilumab vs. placebo for patients with COPD (ITT population) in the BOREAS trial

Outcome measure	Dupilumab (N=468)	Placebo (N=471)	Results
Annualized rate of moderate or severe COPD exacerbations at week 52	0.78 (95% CI: 0.64, 0.93)	1.10 (95% CI: 0.93, 1.30)	Absolute risk: -0.33 (95% CI: -0.46, -0.15) Relative risk: 0.70 (95% CI: 0.58, 0.86)
Change in pre-bronchodilator FEV_1 from baseline to week 52	0.153 (95% CI: 0.116, 0.189)	0.070 (95% CI: 0.033, 0.107)	LSM: 0.083 (95% CI: 0.038, 0.128)

Abbreviations: LSM: Least-square mean, FEV1: Forced expiratory volume in 1 Second, ppb: parts per billion.

6.1.5 Efficacy – results per NOTUS

In the following, efficacy results from the ITT population in the NOTUS trial are presented. For the change in pre-bronchodilator FEV_1 from baseline to week 52, results from the ITT with the opportunity to reach 52 week was available and presented.

6.1.5.1 Annualized rate of moderate or severe COPD exacerbations

In the NOTUS trial, dupilumab led to a statistically significant and clinically meaningful reduction in the annualized rate of moderate or severe COPD exacerbations during the 52-week trial period. The rate in the dupilumab group was 0.859 (95% CI: 0.699, 1.057) compared to 1.295 (95% CI: 1.048, 1.600) in the placebo group. The relative risk was

0.664 (95% CI: 0.535, 0.823, p = 0.0002) (6). The cumulative mean number of moderate or severe COPD exacerbations from the ITT population is presented in Figure 10.

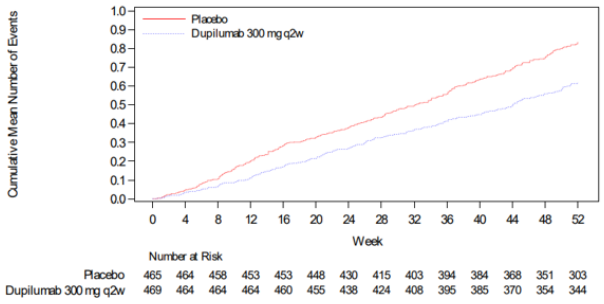


Figure 10: Cumulative mean number of moderate or severe COPD exacerbations during the 52-week treatment period. Source: Bhatt et al. 2024 (6).

6.1.5.2 Change in pre-bronchodilator FEV_1 from baseline to week 52

At baseline, in the ITT population with an opportunity to reach week 52, the mean (SD) in pre-bronchodilator FEV1 in the dupilumab group was 1.36 (0.49) and 1.40 (0.49) in the placebo group. At week 52, the mean (SD) was 1.47 (0.61) in the dupilumab group and 1.46 (0.58) in the placebo group. Dupilumab resulted in statistically significant and clinically meaningful improvement in pre-bronchodilator FEV_1 at week 52 compared to placebo. The LS mean change from baseline to week 52 was +0.115 (SE: 0.021, 95% CI: 0.074, 0.156) liter in the dupilumab group compared to +0.054 (SE: 0.020, 95% CI: 0.015, 0.093) liter in the placebo group. The LS mean difference was +0.062 liter (95% CI: 0.011, 0.113, p =0.0182). Results are presented and summarised in Figure 11 and Table 14.

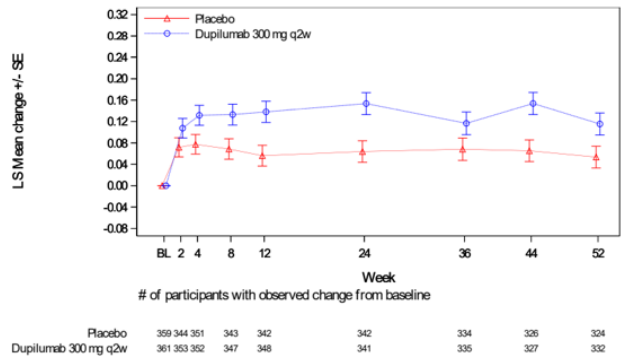


Figure 11: LS mean change from baseline in pre-bronchodilator FEV_1 in liters up to week 52 among patients with the opportunity to reach week 52. Source: Bhatt et al. 2024 (6).

Table 14 Results from the comparative analyses of dupilumab vs. placebo for patients with COPD (ITT population) in the NOTUS trial

Outcome measure	Dupilumab (N=470)	Placebo (N=465)	Result
Annualised rate of moderate or severe COPD exacerbations at week 52	ITT (n=470): 0.859 (95% CI: 0.699, 1.057)	ITT (n=465): 1.295 (95% CI: 1.048, 1.600)	Absolute risk: -0.435 (95% CI: -0.602, -0.229) Relative risk: 0.664 (95% CI: 0.535, 0.823)
Change in pre-bronchodilator FEV_1 from baseline to week 52	ITT with the opportunity to reach 52 weeks (n=362): +0.115 (SE: 0.021, 95% CI: 0.074, 0.156) liter	ITT with the opportunity to reach 52 weeks (n=359): +0.054 (SE: 0.020, 95% CI: 0.015, 0.093) liter	The LS mean difference: +0.062 liter (95% CI: 0.011, 0.113, p =0.0182)

Abbreviations: LSM: Least-square mean, FEV1: Forced expiratory volume in 1 Second, ppb: parts per billion, SE: standard error, ITT: intent-to-treat.

6.1.6 Pooled results from BOREAS and NOTUS

A total of 1,874 participants were randomised across the two pivotal studies: 938 in the pooled dupilumab group and 936 in the pooled placebo group. The absence of heterogeneity between the BOREAS and NOTUS studies, along with the consistent efficacy results observed for both studies, allowed a valid and interpretable pooled analyses of the efficacy data to be conducted. Replication of efficacy was demonstrated in the pooled analysis with statistically significant and clinically meaningful improvements observed for dupilumab compared to placebo.

Compared to placebo, dupilumab demonstrated a significant reduction in the annualized rate of moderate or severe exacerbations and a significant and rapid improvement in pre-BD FEV1 at week 12 that was maintained at week 52: in the pooled ITT population, the adjusted annualised rate of moderate or severe exacerbation events over the 52-week intervention period was 0.794 (95% CI: 0.686, 0.920) in the dupilumab group versus 1.156 (95% CI: 1.005, 1.330) in the placebo group. This represents a clinically meaningful reduction of 31% in the annualised rate of moderate or severe exacerbation events as compared to placebo (nominal p<0.0001). The mean baseline pre-bronchodilator FEV1 was 1.32 (SD: 0.47, 95% CI: 1.29, 1.35) in the dupilumab group and 1.35 (SD: 0.48, 95% CI: 1.32, 1.38) in the placebo group. At week 52, it was 1.45 (SD: 0.59, 95% CI: 1.41, 1.49) in the dupilumab group and 1.42 (SD: 0.55, 95% CI: 1.38, 1.46) in the placebo group. The LS mean change in pre-BD FEV_1 from baseline to week 52 was +0.133 L (95% CI: 0.104, 0.162) in the dupilumab group and +0.059 L (95% CI: 0.030, 0.088) in the placebo group, resulting in an LS mean difference versus placebo of +0.073 L (95% CI: 0.040, 0.107, nominal p<0.0001). The improvement in pre-BD FEV_1 is illustrated in Figure 12 and results are presented in Table 15.

Figure 12: LS mean change from baseline in pre-bronchodilator FEV_1 up to week 52 in the pooled analysis. Source: Sanofi data on file.

Table 15 Results from the comparative analyses of dupilumab vs. placebo for patients with COPD (ITT) in the pooled analysis of BOREAS and NOTUS. Source: Sanofi data on file.

Outcome measure	Dupilumab (N=938)	Placebo (N=936)	Result
Annualised rate of moderate or severe COPD exacerbations at week 52	0.794 (95% CI: 0.686, 0.920)	1.156 (95% CI: 1.005, 1.330)	Absolute risk: -0.362 (95% CI: -0.468, -0.239) Relative risk: 0.687 (95% CI: 0.595, 0.793), <.0001
Change in pre-bronchodilator FEV_1 from baseline to week 52	ITT with the opportunity to reach 52 weeks (n=830)* 0.133 (SE: 0.015, (95% CI: 0.104, 0.162)	ITT with the opportunity to reach 52 weeks (n=830) 0.059 (SE: 0.015, (95% CI: 0.030, 0.088)	LS mean difference: 0.073 (95% CI: 0.040, 0.107), <.0001

Abbreviations: LSM: Least-square mean, FEV1: Forced expiratory volume in 1 Second, ppb: parts per billion, SE: standard error, ITT: intent-to-treat.*two participants were not exposed to study intervention in the NOTUS study.

7. Comparative analyses of efficacy

The BOREAS and NOTUS trials are both head-to-head trials of dupilumab compared to placebo with data on all relevant outcomes. Thus, no comparative analyses are presented in this section in accordance with DMC method guideline. Please see section 6 for comparative results.

7.1.1 Differences in definitions of outcomes between studies

N/A

7.1.2 Method of synthesis

N/A

7.1.3 Results from the comparative analysis

N/A

7.1.4 Efficacy – results per [outcome measure]

N/A

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

This section presents how efficacy has been modelled in the health economic analysis and how the transition probabilities for the Markov model have been derived. Table 16 presents a summary of the clinical inputs used in the Markov model.

Table 16 Summary clinical inputs used in the model

Clinical input	Input source	Options in the model
Distribution of patients by GOLD Severity	Trial based input for baseline from week 2 and week 52 were derived from Sanofi statistical analysis of pooled data (data on file) or BOREAS and NOTUS separately for the ITT population.	- User-defined option: In the base case, the distribution of patients was set to: Moderate COPD: 50% Severe COPD: 50% to reflect the relevant Danish population. - Trial-based option: based on Sanofi statistical analysis of pooled data (data on file) or BOREAS and NOTUS separately.
Responder rates		Not applied to background therapy. Not included for dupilumab in the base case.
Exacerbation rates		Selected trial: Treatment-specific inputs or relative risk
Distribution of patients by number of exacerbations		Trial-based inputs

Transition probabilities within COPD stage	Derived from Sanofi statistical analysis of pooled data (data on file) and Whittaker 2022 (7)	- Disabled (base case) - Trial-based - Derived from Whittaker 2022 (7) - For dupilumab, same as above or apply relative risk
Transition probabilities across COPD stage		- Within treatment effect period: trial-based inputs (Disabled in base case) - Beyond treatment effect period: Fenwick 2021 (8)
Treatment discontinuation rates	Derived from Sanofi statistical analysis of pooled data (data on file) and validated by the clinical expert	- Trial-based inputs as validated by Danish clinical expert
Treatment effect duration	TRAVERSE open label extension study and assumption	- For dupilumab and background therapy, the extended FEV1 treatment effect beyond the observed trial data was set to 2 years in line with the findings in the TRAVERSE study (treatment with dupilumab in moderate-to-severe asthma) (53). As the improvenment in FEV1 was disabled this input meant that deterioration of lung function was postponed for 2 years. For background therapy only, the extended treatment effect of placebo is assumed to be 0 years. See the "General inputs" sheet.

For dupilumab and background therapy, in the base case, clinical data were informed by a post hoc analysis of pooled patient-level data from the BOREAS and NOTUS trials (Sanofi data on file). A separate statistical analysis plan was developed to derive clinical outcomes required by the model, e.g., exacerbation rates, FEV_1 change over time, GOLD distribution during the trial period.

Table 17 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
Across COPD stages			
Mild COPD	Mild COPD		

	Moderate COPD	Based on pooled BOREAS/NOTUS trial and Fenwick et al. 2021 (8). (Disabled in base case) Sepeated into treatment effect period (pooled analysis) and beyond treatment effect period (Fenwick et al. 2021). In the treatment effect period, since the trial data showed the improvement in lung function was observed within 2 weeks after the initiation dupilumab or background therapy and was sustained through week 52, it was assumed that the plateau from week 2 to week 52 would be maintained for both treatment arms within the treatment effect period. (Disabled in base case) Thus, no transitions across COPD stage were included in this period. Beyond treatment effect period applied annual probabilities, 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.	Sanofi data on file and Fenwick et al. 2021 (8).
	Severe COPD		
	Very severe COPD		
Moderate COPD	Mild COPD		
	Moderate COPD		
	Severe COPD		
	Very severe COPD		
Severe COPD	Mild COPD		
	Moderate COPD		
	Severe COPD		
	Very severe COPD		
Very severe COPD	Mild COPD		
	Moderate COPD		
	Severe COPD		
	Very severe COPD		
Within COPD stages			
No exacerbation	No exacerbation	The transition probabilities were determined by the residing COPD stage and recent exacerbation history (i.e., no exacerbation, moderate exacerbation, or severe exacerbation in the prior year). For background therapy, exacerbation transitions could either be trial based or derived from Whittaker 2022 (7). For dupilumab + background therapy, the relative risk versus background therapy could be	Pooled BOREAS/NOTUS trial or Whittaker 2022.
	≥1 moderate exacerbation		
	≥1 severe exacerbation		
≥1 moderate exacerbation	No exacerbation		
	≥1 moderate exacerbation		

	≥1 severe exacerbation	used. In this case, the exacerbation rates of dupilumab + background therapy was derived by applying relative risk versus background therapy derived from the trials. The rates were then converted to transition probabilities to be used in the model. Other options were trials based or from Whittaker 2022 (7).
≥1 severe exacerbation	No exacerbation	
	≥1 moderate exacerbation	
	≥1 severe exacerbation	

8.1.1 Extrapolation of efficacy data

Not applicable as no extrapolation of efficacy data has been conducted in the model.

8.1.1.1 Extrapolation of [effect measure 1]

Not applicable.

Table 18 Summary of assumptions associated with extrapolation of [effect measure]

Method/approach	Description/assumption
Data input	N/A
Model	N/A
Assumption of proportional hazards between intervention and comparator	N/A
Function with best AIC fit	N/A
Function with best BIC fit	N/A
Function with best visual fit	N/A
Function with best fit according to evaluation of smoothed hazard assumptions	N/A
Validation of selected extrapolated curves (external evidence)	N/A
Function with the best fit according to external evidence	N/A
Selected parametric function in base case analysis	N/A
Adjustment of background mortality with data from Statistics Denmark	N/A
Adjustment for treatment switching/cross-over	N/A

Method/approach	Description/assumption
Assumptions of waning effect	N/A
Assumptions of cure point	N/A

8.1.1.2 Extrapolation of [effect measure 2]

N/A

8.1.2 Calculation of transition probabilities

The distribution of patients by GOLD severity at end of the FEV_1 amelioration phase (i.e., week 2) and end of the FEV_1 maintenance phase (i.e., week 52) in the decision tree component of the model was derived for the ITT by treatment arm. The baseline distribution was based on the average of the two arms combined. The distributions are presented in Table 19 but not used in the base case where FEV_1 amelioration is disabled.

Table 19 Distribution of patients by GOLD severity and treatment (ITT population). Source: Sanofi data on file.

Timepoint	Dupilumab + background therapy				Background therapy			
	Mild	Moderate	Severe	Very Severe	Mild	Moderate	Severe	Very Severe
Baseline	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx
Week 2 (amelioration phase)	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx
Week 52 (maintenance phase)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx

Abbreviations: GOLD = Global Initiative for Chronic Obstructive Lung Disease; ppb = parts per billion; ITT = intent to treat. Please find these distributions in the 'Dupilumab Trial inputs' sheet in the model.

The model provides the flexibility to allow patients to start at different GOLD stages from the trial population (i.e., user-defined GOLD distribution at baseline). The conditional probabilities based on GOLD severity at week 2 derived from trials were applied to project the cohort's distribution by GOLD severity at week 2. For the maintenance stage (from week 2 to 52), no change of GOLD severity was assumed.

Table 20 Conditional probabilities by GOLD severity at week 2 (ITT population). Source: Sanofi data on file.

Start Sate	End state	
	Dupilumab + background therapy	Background therapy

	Mild	Moderate	Severe	Very Severe	Mild	Moderate	Severe	Very Severe
Mild	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
Moderate	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
Severe	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
Very severe	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx

Abbreviations: GOLD = Global Initiative for Chronic Obstructive Lung Disease; ITT = intent to treat. Please find these probabilities in the 'Trial period' sheet in the model.

In the base case, user-defined baseline values were chosen to better reflect the relevant Danish population (50% moderate and 50% severe COPD). As a result, the patients were evenly split between the moderate GOLD stage and the severe GOLD stage for both dupilumab + background therapy and background therapy.

Table 21 Base case distribution of patients by GOLD severity and treatment (ITT population). Source: Sanofi data on file and user-defined input.

Timepoint	Dupilumab + background therapy				Background therapy			
	Mild	Moderate	Severe	Very Severe	Mild	Moderate	Severe	Very Severe
Baseline	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx
Week 2 (amelioration phase)	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx
Week 52 (maintenance phase)	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx

Abbreviations: GOLD = Global Initiative for Chronic Obstructive Lung Disease; ppb = parts per billion; ITT = intent to treat. Please find these distributions in the 'Trial inputs' sheet in the model.

8.1.2.1 Response rates

A responder was defined as a patient with reduction of annualised rate in severe exacerbation ≥0% compared with the prior number of severe exacerbations in the year before randomisation or reduction of annualised rate in moderate or severe exacerbation ≥0% compared with the prior number of moderate or severe exacerbations in the year before randomization. Other cases were considered non-responders. With this response definition, the response rate among patients who received dupilumab + background therapy in the pooled trials at the end of week 52 was xxxx for the ITT population.

The model provides the option to apply response assessment at the end of week 52 after initiation of dupilumab, assuming responders would continue receiving dupilumab + background therapy, while non-responders would switch to receive background therapy only. After week 52, clinical outcomes specific to responders derived from the pooled trials were applied if response assessment was selected. Otherwise, clinical outcomes for all patients were be applied. Clinical outcomes related to background therapy were applied to non-responders. Response assessment was not applied in the background therapy arm. In the base case, no response assessment was applied.

It is important to note that the decision tree part of the model does not include increasing or compounding risks of exacerbations as shown in section 3.1.2, whereas the Markov part of the model does. As described in section 3.1.2, exacerbations increase in frequency and severity over time and patients with COPD in the GOLD E category are expected to experience rather frequent and severe exacerbations. An evaluation of a response to dupilumab treatment would need to take this increase into account. Indeed, a stabilization or reduction in frequency and/or severity of exacerbations would be an important improvement for the patient.

8.1.2.2 Exacerbation rates in the model

Exacerbation rates were informed by the pooled BOREAS and NOTUS trials either using: 1) trial-observed exacerbation rates specific to the treatment or 2) relative risk for exacerbation of dupilumab + background therapy versus background therapy.

Given the small number of patients with ≥1 moderate or severe exacerbation event within the first 52 weeks from the pooled trials in the mild and very severe COPD stage (~20 in either stage in each arm), trial-observed annualised exacerbation rates presented in Table 22 were not further adjusted to account for the potential confounders (e.g., baseline disease severity, smoking status at screening, number of exacerbations within 1 year before the study). Hence, unadjusted annualised rates were directly used, also to estimate the relative risk of dupilumab + background therapy versus background therapy (see Table 23). The input for dupilumab + background therapy was specific to all patients and responders only.

Table 22 Annualised exacerbation rates by GOLD severity and treatment (ITT population). Source: Sanofi data on file.

GOLD stage	Dupilumab + background therapy				Background therapy	
	All Patients		Responders (not included in the base case)			
	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: GOLD = Global Initiative for Chronic Obstructive Lung Disease; ppb = parts per billion.
Please find these rates in the "General inputs" sheet in the model.

Table 23 Relative risk for exacerbation by GOLD severity of dupilumab + background therapy vs background therapy (ITT population). Source: Sanofi data on file.

GOLD Stage	Dupilumab + Background therapy			
	All Patients		Responders (not included in the base case)	
	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]

Abbreviations: GOLD = Global Initiative for Chronic Obstructive Lung Disease; ppb = parts per billion.
Please find the relative risks in the "General inputs" sheet within the model.

8.1.2.3 Distribution of patients by number of exacerbations

Since patients may experience more than one moderate or severe exacerbation within one model cycle as the cycle length is 1 year, patients residing in the 'Moderate Exacerbation' or 'Severe Exacerbation' health states in the model were further stratified by the number of exacerbations (1, 2, or 3+) to better capture costs and disutilities associated with exacerbation. The distribution of patients experiencing different number of exacerbation events within the first 52 weeks was derived from the pooled trials, please see Table 24.

Table 24 Distribution of patients by number of exacerbations by treatment (ITT population). Source: Sanofi data on file.

No. of exacerbations	Dupilumab + Background therapy				Background therapy	
	All patients		Responders (not included in the base case)			
	Moderate exacerbation	Severe exacerbation	Moderate exacerbation	Severe exacerbation	Moderate exacerbation	Severe exacerbation
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

In addition, trial data were used to estimate the average number of exacerbations for patients who have ≥3 exacerbations. As patients who were assigned to the severe exacerbation category may also experience moderate exacerbations, the average number was also informed by the trial data, please see Table 25.

Table 25 Average number of exacerbations for each exacerbation state. Source: Sanofi data on file.

Sub-state defined by No. of exacerbations	No. of moderate exacerbations	Source	No. of severe exacerbations	Source
1 Moderate only	[redacted]	Assumption to reflect the definition of the substate	[redacted]	Assumption to reflect the definition of the substate
2 Moderate only	[redacted]		[redacted]	
≥3 Moderate only	[redacted]	Pooled trials	[redacted]	
1 Severe	[redacted]		[redacted]	
2 Severe	[redacted]		[redacted]	
≥3 Severe	[redacted]		[redacted]	Pooled trials

8.1.2.4 Transition probabilities within COPD states (based on exacerbations)

Within each COPD stage, patients could experience no exacerbation, ≥1 moderate exacerbation (without severe), or ≥1 severe exacerbation in a given cycle. The transition probabilities were determined by the residing COPD stage and the patient's recent exacerbation history (i.e., no exacerbation, moderate exacerbation, or severe exacerbation in the prior year). For background therapy, there were two options to inform exacerbation transitions within COPD stages:

- Option 1: Trial-based probabilities (used in our base case): Directly derived from the selected trial. The transitions were stratified based on the GOLD stage and the status of recent exacerbation (no exacerbation, ≥1 moderate exacerbation, or ≥1 severe exacerbation).
- Option 2: Derived from Whittaker 2022: Based on the specified exacerbation rate at baseline and adjusted IRR from Whittaker 2022 separate for moderate and severe by number of exacerbations occurred within a prior year.

For dupilumab + background therapy, the following options were considered:

- Option 1: Relative risk versus background therapy: In this case, the exacerbation rates of dupilumab + background therapy was derived by applying relative risk versus background therapy derived from the trials (see Table 23). The rates were then converted to transition probabilities to be used in the model.
- Option 2 and 3: Same two approaches as background therapy as described above.

The treatment-specific exacerbation rates were applied throughout the time horizon. Thus, there was no maximum treatment effect period applied to exacerbation rates,

assuming they were driven by patient's GOLD stage (indirectly through treatment effect on FEV_1 decline). The options are described in the following.

8.1.2.4.1 Trial-based exacerbation probabilities (from BOREAS and NOTUS)

The percentages of patients experiencing no exacerbation, ≥1 moderate exacerbation (without severe), or ≥1 severe exacerbation within each GOLD stage could be derived from the pooled trials. Since the Markov model considers health states associated with the severity of recent exacerbations, we needed to derive the corresponding transition probabilities. In the clinical trials of dupilumab, patients need to have had at least 2 moderate or 1 severe prior exacerbation in the year prior to randomization. Thus, by definition, the transition probabilities of patients with no prior exacerbation cannot be estimated from the trial. To do this, IRRs from Whittaker 2022 were used with '2 moderate exacerbations' as the new reference for the incidence rate ratio. The estimates are presented in Table 26.

The revised ratios were applied to the trial data to generate annual probabilities of experiencing exacerbations within COPD stage for the ITT population, which are presented in
Table 27 and Table 28 for dupilumab and background therapy for the ITT population, respectively. These transition probabilities were applied in the base case.

Table 26 Revised IRR for future moderate and severe exacerbation by baseline frequency and severity of exacerbation. Source: Whittaker 2022.

Prior exacerbation status	IRRs for moderate exacerbation		IRRs for severe exacerbation	
	From Whittaker 2022	Revised	From Whittaker 2022	Revised
No exacerbation	1 (ref)	0.41 (1/2.44)	1 (ref)	0.72 (1/1.38)
2 moderate exacerbations only	2.44	1 (ref)	1.38	1 (ref)
1 severe exacerbation	2.48	1.02 (2.48/2.44)	2.66	1.9 (2.66/1.38)

Abbreviation: IRR = incidence rate ratio

Table 27 Annual transition probabilities within COPD stage for dupilumab based on trials. All patients and responders (ITT population). Source: Sanofi data on file.

From State		Exacerbation events in a given cycle (%)					
COPD state	Exacerbation state	Dupilumab all patients			Dupilumab responders		
		No Exac.	≥ 1 Mod Exac.	≥ 1 Sev Exac.	No Exac.	≥ 1 Mod Exac.	≥ 1 Sev Exac.

Mild COPD	No Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate COPD	No Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe COPD	No Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Very Severe COPD	No Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The probabilities are calculated in the "Dupilumab Trial inputs" sheet in the model if the source of the exacerbation rate of comparators in sheet "General inputs" is set to *Selected trial*.

Table 28 Annual transition probabilities within COPD stage for backgorund therapy for ITT (based on trial). Source: Sanofi data on file.

From State		Exacerbation events in a given cycle (%)		
COPD state	**Exacerbation state**	**No exac.**	**≥ 1 Mod exac.**	**≥ 1 Sev exac.**
Mild COPD	No Exacerbation	[redacted]	[redacted]	[redacted]
	Moderate Exacerbation	[redacted]	[redacted]	[redacted]
	Severe Exacerbation	[redacted]	[redacted]	[redacted]
Moderate COPD	No Exacerbation	[redacted]	[redacted]	[redacted]
	Moderate Exacerbation	[redacted]	[redacted]	[redacted]
	Severe Exacerbation	[redacted]	[redacted]	[redacted]
Severe COPD	No Exacerbation	[redacted]	[redacted]	[redacted]
	Moderate Exacerbation	[redacted]	[redacted]	[redacted]
	Severe Exacerbation	[redacted]	[redacted]	[redacted]
Very Severe COPD	No Exacerbation	[redacted]	[redacted]	[redacted]
	Moderate Exacerbation	[redacted]	[redacted]	[redacted]
	Severe Exacerbation	[redacted]	[redacted]	[redacted]

Please find the probabilities in the "Markov transitions" sheet in the model.

8.1.2.4.2 Relative risks to generate exacerbation rates

An alternative option to generate exacerbation rates for dupilumab + background was to apply the relative risks for dupilumab versus background therapy presented in Table 23 obtained from the trial period to the revised exacerbation rates for background therapy as described above. The transition probabilities based on the relative risk are presented in Table 29.

Table 29 Annual transition probabilities within COPD stage for dupilumab + background therapy. All patients and repsonders for ITT (relative risk based). Source: Sanofi data on file.

From State	Exacerbation events in a given cycle (%)			
COPD State	Exacerbation state	Dupilumab all patients		
		No Exac.	≥1 Mod Exac.	≥1 Sev Exac.
Mild COPD	No Exacerbation	[redacted]	[redacted]	[redacted]
	Moderate Exacerbation	[redacted]	[redacted]	[redacted]
	Severe Exacerbation	[redacted]	[redacted]	[redacted]
Moderate COPD	No Exacerbation	[redacted]	[redacted]	[redacted]
	Moderate Exacerbation	[redacted]	[redacted]	[redacted]
	Severe Exacerbation	[redacted]	[redacted]	[redacted]
Severe COPD	No Exacerbation	[redacted]	[redacted]	[redacted]
	Moderate Exacerbation	[redacted]	[redacted]	[redacted]
	Severe Exacerbation	[redacted]	[redacted]	[redacted]
Very Severe COPD	No Exacerbation	[redacted]	[redacted]	[redacted]
	Moderate Exacerbation	[redacted]	[redacted]	[redacted]
	Severe Exacerbation	[redacted]	[redacted]	[redacted]

The probabilities are calculated in the "Dupilumab Trial inputs" sheet in the model if the source of the exacerbation rate of comparators in sheet "General inputs" is set to *RR vs SoC*.

8.1.2.4.3 Exacerbation probabilities derived from Whittaker 2022

An alternative option to generate exacerbation probabilities was Whittaker 2022 (7). This can be chosen in the model ("Markov transitions"-sheet).

8.1.2.5 Transition probabilities across COPD states (based on FEV_1 decline)

8.1.2.5.1 Transitions within the treatment effect period

The follow-up period for the BOREAS and NOTUS trials extended up to 52 weeks; thus, it is currently uncertain if the benefit of dupilumab is maintained long-term. In the model, the duration of extended treatment effect period after 52 weeks is user-modifiable. In the base case this was disabled. After the trial period, it was assumed that treatment effect may be retained for a longer time for patients who continuously receive the treatment. Since the trial data shows the improvement in lung function was observed within 2 weeks after the initiation dupilumab or background therapy and was sustained

through week 52 (as shown in Figure 9), it was assumed that the plateau from week 2 to week 52 would be maintained for both treatment arms within the treatment effect period i.e., there were no transitions across COPD stage.

8.1.2.5.2 Transitions beyond the treatment effect period

Beyond the treatment effect period, transitions between COPD stages were informed by the annual probabilities reported by Fenwick et al. 2021 (8), which were based on statistical equations for FEV_1 decline over time using data from the 3-year TORCH study. The transition probabilities presented in Table 30 were equally applied to both arms.

Table 30 Annual transition probabilities across COPD stage beyond the treatment effect period. Source: Fenwick et al. 2021 (8).

Transition between COPD stage	Exacerbation status	Annual transition probabilities
Mild COPD to moderate COPD	No Exacerbation	4.1%
	Moderate Exacerbation	8.8%
	Severe Exacerbation	8.8%
Moderate COPD to severe COPD	No Exacerbation	4.1%
	Moderate Exacerbation	8.8%
	Severe Exacerbation	8.8%
Severe COPD to very severe COPD	No Exacerbation	7.0%
	Moderate Exacerbation	14.3%
	Severe Exacerbation	14.3%

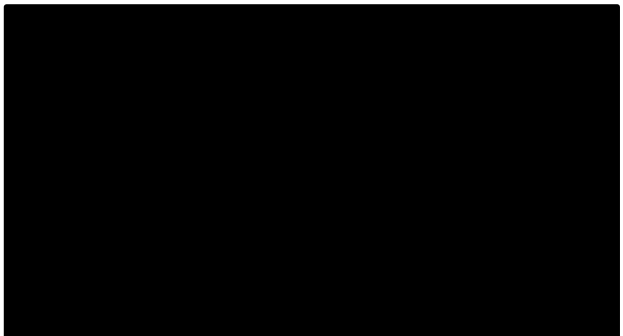
Abbreviation: COPD = chronic obstructive pulmonary disease.
Due to lack of transition probabilities from mild COPD to moderate COPD, inputs for transition from moderate COPD to severe COPD were applied. Transition probabilities from the source were not differentiated by exacerbation severity (i.e., moderate or severe), therefore, the probabilities with recent exacerbation history were applied regardless of exacerbation severity.

8.1.3 Discontinuation of dupilumab within and beyond the trial period

In addition to response stratification, patients receiving dupilumab treatment could discontinue dupilumab and switch to receiving only background therapy. For simplicity, since the decision tree component did not have a cycle length, it was assumed that the treatment discontinuation was applied as a one-off at the end of week 52. This was a conservative assumption as patients who discontinued in the first year still accrued costs for dupilumab until the end of week 52. Beyond week 52, the discontinuers received only the background therapy in the Markov model.

Based on the pooled trial outcomes, xxxx of the patients in the dupilumab group completed the 52-week trial period. Therefore, xxx of treatment discontinuation was applied for the trial period. Beyond the trial period (52 weeks), the discontinuation rate was set to xxx as informed by the Danish clinical expert.

Figure 13 Proportion of patients in each health state in the mode



8.1.4 Mortality in the model

There is a significant excess mortality associated with COPD compared to the general population and therefore, it is imperative for the model to capture the mortality risk associated with COPD in an accurate fashion. The excess mortality is linked to the COPD stages and severe exacerbations, but studies have indicated that patients' recent exacerbation status (no exacerbation, moderate exacerbation, and severe exacerbation) as well as the number of recent exacerbations influence all-cause mortality (8,54,55). Thus, the model aimed to capture the increased mortality due to GOLD stages and exacerbations separately via standardized mortality ratio (SMR) and incidence rate ratios (IRR) that are relative to the general population mortality derived from Danish lifetables. The general population mortality directly derived from Danish lifetables.

8.1.4.1 Excess mortality associated with COPD stage

Danish mortality data associated with COPD stage could not be identified. Thus, the excess mortality associated with COPD stage was derived from Shavelle et al. (50). This excess mortality is modelled via an SMR for individual COPD stages without exacerbation history, and this SMR is applied vs the adjusted general population mortality. Since the study did not report the SMR associated with mild COPD, it was assumed that the mild COPD patients have an SMR of 1.0 (equivalent to adjusted general population). In addition, Shavelle et al. (50) reported an SMR of 2.6 for severe COPD patients and did not report the SMR separately for severe and very severe COPD stages. It was assumed that the SMR of severe COPD was 2.55 and 2.65 whereas the reported value was 2.6 (see Table 31). This assumption has been tested in the scenario analysis. In addition to the original SMRs reported by Shavelle et al. (50), an adjustment in the base case was made in order to reflect the considerably higher mortality in the Danish moderate and severe COPD population in ambulatory care based on Waeijen-Smit et al. (32). Please see section 8.1.4.3.

Table 31 Excess mortality due to COPD stage, without exacerbation history.

COPD Severity	SMR (pre-adjustment)	SMR (post-adjustment)
Mild COPD	1	2.0
Moderate COPD	1.4	2.8
Severe COPD	2.55	5.1
Very Severe COPD	2.65	5.3

Abbreviations: COPD = chronic obstructive pulmonary disease; SMR = standardized mortality ratio

8.1.4.2 Excess mortality associated with exacerbations

In addition to excess mortality due to COPD stage, excess mortality due to recent exacerbations was applied as an IRR vs a patient who experience no recent exacerbations (54). In addition to the original IRRs reported by Whittaker et al. (54), adjustment to the reported IRRs was done for the base case, in order to reflect the considerably higher mortality in the Danish moderate and severe COPD population in ambulatory care based on Waeijen-Smit et al. (32). Please see section 8.1.4.3.

Table 32 shows the excess mortality modelled due to the severity as well as the frequency of exacerbation events. Both pre-adjustment and post-adjustment excess mortality rates are reported.

Table 32 Excess mortality due to COPD stage, without exacerbation history

Exacerbation type	Exacerbation frequency	Excess mortality, IRR (pre-adjustment)	Excess mortality, IRR (post-adjustment)
Moderate[a]	1	1.08	3.62
	2	1.16	3.89
	3+	1.32	4.42
Severe	1	1.75	5.86
	2	2.33	7.81
	3+	2.87	9.61

Abbreviation: IRR = incident rate ratio.
[a]Patients with moderate exacerbation do not experience any severe exacerbations.

It is noted that the excess mortality associated with COPD stage and exacerbation events have been derived from different sources. Even though the excess mortality due to exacerbation was said to be adjusted in the Whittaker study, it is unclear how these adjustments were made. This uncertainty could lead to potential overestimation of the effect of mortality and therefore handled via a scenario analysis where the model considered only the effect of excess mortality due to COPD stages and only excess mortality due to exacerbations.

Secondly, the Markov model only considered the probability of patients experiencing no exacerbation, at least 1 moderate exacerbation (no severe), and at least 1 severe exacerbation. Once patients experienced an exacerbation event (moderate/severe), they were divided into 1,2, and 3+ exacerbations via a proportion derived from the selected trial population, which was assumed to be constant throughout the model horizon. It is clear that the number of exacerbations play a significant role on mortality, and dividing the patients into 1,2, and 3+ exacerbations must be considered. Since there currently are no long-term data to inform this distribution beyond the observed trial period of 1 year, the model assumed that the distribution of patients (1,2, and 3+ exacerbations) observed in the selected trial remained constant throughout the horizon.

8.1.4.3 Adjustments made to reflect mortality in the Danish setting

If the model is based only on unadjusted SMRs based on Shavelle et al. (50) and IRRs for exacerbations based on unadjusted estimates from Whittaker et al. (54) the 5-year mortality is 16%. By contrast the 5-year mortality of the general population, estimated by setting all SMRs and IRRs to 1, is 7%. In a recent study published by Waeijen-Smit et al. (32) the 5-year mortality was estimated at 58%, following the first ever severe exacerbation in Danish patients in ambulatory care. The clinical expert states that the most common way of inclusion in ambulatory care in Denmark is after hospitalization with an exacerbation. The modeled proportion of mortality from exacerbations in the unadjusted setting with SMRs based on Shavelle et al. and IRRs for exacerbations based on unadjusted estimates from Whittaker et al. is 13%. If adjustments are only made to

SMRs by GOLD stages due to the relative nature of the IRRs for exacerbations this proportion remains constant.

To adjust the modeled excess mortality from COPD stage and exacerbations in the model, a systematic literature review was conducted to base assumptions on the relative distribution of causes of death in moderate and severe COPD (see section J.2.3). As the model includes two causes of death; exacerbations and any other cause, the relative proportion of respiratory causes of death was of considerable interest. In addition to cause of death that are directly classified as respiratory, according to input from the clinical expert, there is a well-researched link between exacerbations and other causes. Especially there is a link to major cardiovascular events and cardiovascular mortality documented in Danish patients in ambulatory care (56), lung cancer where exacerbations might not be classified as the cause of death.

The literature review found 7 studies that reported causes of death based on lung function; mild, moderate, sever and very severe. The synthesis of the review showed that there is a considerable gradient of respiratory and all-cause mortality to lung function and that there is a strong relation between follow up time in studies and respiratory mortality, where lower lung function and longer follow-up is associated with very high proportions of respiratory mortality.

In a 10.1-year median follow-up study Labaki et. al 2023 (57) found that the proportion of deaths from respiratory causes was highly determined by lung function, with GOLD 1-2 vs. GOLD 3-4 (incidence rate %, (P value)) 19.8% vs. 61.5% (P<0.001) for respiratory causes, 22.5% vs. 10.1% (P<0.001) for cardiovascular causes and 18.3% vs. 9.3% (P<0.001) for lung cancer.

Bale et al. 2008 (58) reported based on the Inhaled Steroids in Obstructive Lung Disease (ISOLDE) at various follow up times for moderate and severe COPD patients. At 13 years causes of death were; 52% respiratory, 18% cardiac, 14% lung cancer, 8% other cancer and 8% other causes. The study clearly demonstrated that the percentage of respiratory-related deaths increased during the follow-up period; from 46% between0- 3 years, 48% between 3-6 years, 57% between 6-9 years, and 60% between 9-13 years of follow-up (p for trend<0.05).

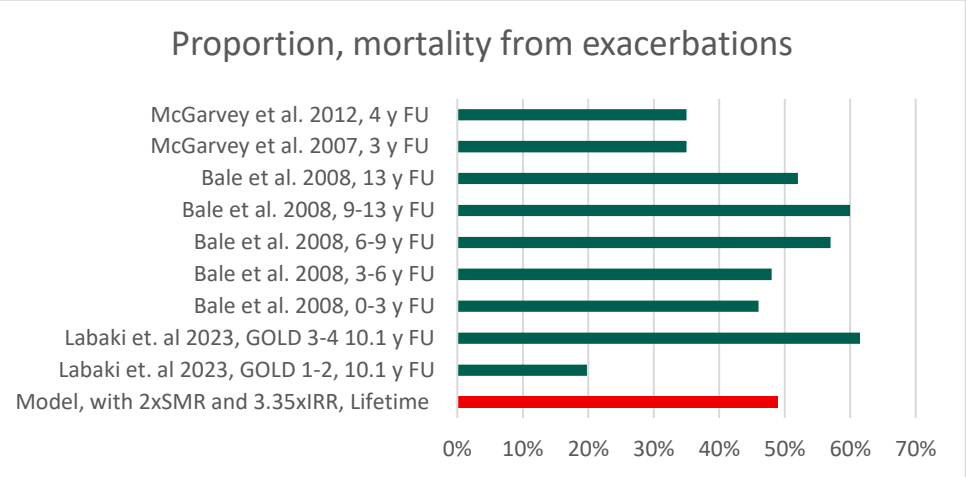
McGarvey et al. 2007 (59) investigated cause-specific mortality in moderate and severe COPD patients based on the TORCH study after 3 years follow-up. They found mortality proportions; cardiovascular 27%, respiratory 35%, cancer 21%, other 10% and unknown 8%.

McGarvey et al. 2012 (60) investigated cause-specific mortality in moderate and severe COPD patients based on the UPLIFT trial. Overall findings after 4 years and 30 days follow-up was; respiratory, 35%; cancer, 25%; cardiovascular, 11%; sudden cardiac death, 4.4%; sudden death, 3.4%; other, 8.8%; unknown, 12.4%. The study also reported causes broken down by lung function and found that respiratory causes were found in 16.8%, 37.5% and 59.0% in subjects with GOLD 2, 3 and 4 respectively, demonstrating a clear gradient between lung function and respiratory death at 4 years and 30 days.

Based on these findings from the systematic literature review in section J.2.3, the base case adjustments made to SMRs and IRRs respectively are 2XSMR and 3.35XIRR 6 (see

Table 32 and Table 31). This setting means that the modelled 5-year mortality is 58%. The modeled proportion of mortality from exacerbations is 49% with this setting.

Figure 14 proportion of mortality from exacerbations, selected studies and model settings



These assumptions are deemed justified due to the life-time perspective of the model and the severity of the Danish COPD patients treated in the Danish ambulatory setting with very high 5-year mortality. With these adjustments to the model, it predicts 1-year mortality in the background therapy at 16% and in comparison, it should be noted that the DrKOL data of moderate and severe COPD patients in ambulatory care show that the 1-year mortality is 25.1%.

8.2 Presentation of efficacy data from [additional documentation]

Not applicable.

8.3 Modelling effects of subsequent treatments

Not applicable as not subsequent treatments were included.

8.4 Other assumptions regarding efficacy in the model

Not applicable.

8.5 Overview of modelled average treatment length and time in model health state

Estimates for the modelled average and modelled median of the effect measures predicted by the extrapolation model were not presented, as no extrapolation was conducted in the health economic analysis. Table 34 provides the modelled average treatment length and time in model health states.

Table 33 Estimates in the model N/A

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
Dupilumab	N/A	N/A	N/A
Background therapy	N/A	N/A	N/A

Table 34 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction [years]

Treatment	Treatment length	Mild COPD	Moderate COPD	Severe COPD	Very severe COPD
Dupilumab	4.95	0.00	2.40	2.09	0.46
Background therapy	4.15	0.00	1.89	1.70	0.57

9. Safety

In this section, we present safety data on patients with moderate to severe COPD with type-2 inflammation from the BOREAS and NOTUS trials on dupilumab compared to background therapy.

9.1 Safety data from the clinical documentation

An overview of the safety events in the BOREAS and NOTUS trials is presented in Table 35. In BOREAS, the safety population comprised 469 patients in the dupilumab group and 470 patients in the placebo group (total: 939 patients). The safety population comprised patients who received at least 1 dose of study intervention and patients were analysed according to the intervention actually received. The TEAE period was defined as the period of time form the first administration of study drug to the last administration of study drug plus 98 days. In NOTUS, the safety population comprised 469 patients in the dupilumab group and 464 in the placebo group (total: 933). The safety population and TEAE period were defined as in the BOREAS trial.

Table 35 Overview of safety events in the BOREAS and NOTUS trials at week 52

	The BOREAS trial			The NOTUS trial		
	Dupilumab (N=469) (Bhatt et al. 2023)	**Placebo (N=470) (Bhatt et al. 2023)**	**Difference, % (95 % CI)**	**Dupilumab (N=469) (CSR data on file)**	**Placebo (N=464) (CSR data on file)**	**Difference, % (95 % CI)**
Number of adverse events, n	Not reported	Not reported	N/A	Not reported	Not reported	N/A
Number and proportion of patients with ≥1 adverse events, n (%) Defined as the number of patients with any TEAE TEAEs were defined as AEs that developed or worsened in grade or became serious during treatment period which was defined as the period from the time of first	363 (77.4)	357 (76.0)	1.4% (-4.0%, 6.9%)	313 (66.7%)	306 (65.9%)	0.8% (-5.3%, -6.9%)

	The BOREAS trial			The NOTUS trial		
	Dupilumab (N=469) (Bhatt et al. 2023)	**Placebo (N=470) (Bhatt et al. 2023)**	**Difference, % (95 % CI)**	**Dupilumab (N=469) (CSR data on file)**	**Placebo (N=464) (CSR data on file)**	**Difference, % (95 % CI)**
dose of study treatment until the last visit in the study.						
Number of serious adverse events*, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥ 1 serious adverse events*, n (%) Defined as the number of patients with any treatment-emergent SAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of CTCAE grade ≥ 3 events, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	Not reported	Not reported	N/A	Not reported	Not reported	N/A
Number of adverse reactions, n	Not reported	Not reported	N/A	Not reported	Not reported	N/A
Number and proportion of patients with ≥ 1 adverse reactions, n (%) Defined as the number of patients with any TEAE related to study drug	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number and proportion of patients who had a dose reduction, n (%)	Not reported	Not reported	N/A	Not reported	Not reported	N/A

	The BOREAS trial			The NOTUS trial		
	Dupilumab (N=469) (Bhatt et al. 2023)	**Placebo (N=470) (Bhatt et al. 2023)**	**Difference, % (95 % CI)**	**Dupilumab (N=469) (CSR data on file)**	**Placebo (N=464) (CSR data on file)**	**Difference, % (95 % CI)**
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	xxx	xxx	xxx	xxx	xxx	xxx
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	14 (3.0)	16 (3.4)	-0.4% (-2.7%, 1.8%)	18 (3.8%)	12 (2.6%)	1.3% (-1.0%, 3.5%)

Figuere note: *A serious adverse event were defined as any untoward medical occurrence that at any dose: resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, was a medically important event. Abbreviations: TEAE: treatment-emergent adverse event, CTCAE: Common Terminology Criteria for Adverse Events.

Table 36 presents the frequency of all treatment-emergent adverse events with frequency of ≥ 5% recorded in the BOREAS and NOTUS trials. A list of all serious adverse events observed in BOREAS is presented in Appendix E. Chronic obstructive pulmonary disease was the only serious adverse event with a frecuency of ≥ 5%.

Table 36 Treatment-emergent adverse events in BOREAS and NOTUS (week 52) that occurred with a frequency ≥5% in any treatment group by system organ class and preferred term. Source: Bhatt et al. 2023 supplementary appendix and NOTUS CSR.

	The BOREAS trial				The NOTUS trial			
Adverse events	**Dupilumab (N=469)**		**Placebo (N=470)**		**Dupilumab (N=469)**		**Placebo (N=464)**	
	Number of patients with adverse events	**Number of adverse events**	**Number of patients with adverse events**	**Number of adverse events**	**Number of patients with adverse events**	**Number of adverse events**	**Number of patients with adverse events**	**Number of adverse events**
Adverse event, n (%)	363 (77.6)	Not reported	357 (76.0)	Not reported	313 (66.7)	Not reported	306 (65.9)	Not reported
Nasopharyngitis	44 (9.4)	Not reported	45 (9.6)	Not reported	29 (6.2)	Not reported	24 (5.2)	Not reported
Upper respiratory tract infection	37 (7.9)	Not reported	46 (9.8)	Not reported	N/A	N/A	N/A	N/A
COVID-19	19 (4.1)	Not reported	27 (5.7)	Not reported	44 (9.4)	Not reported	38 (8.2)	Not reported
Headache	38 (8.1)	Not reported	32 (6.8)	Not reported	35 (7.5)	Not reported	30 (6.5)	Not reported
Hypertension	17 (3.6)	Not reported	28 (6.0)	Not reported	N/A	N/A	N/A	N/A
Chronic obstructive pulmonary disease	27 (5.8)	Not reported	28 (6.0)	Not reported	23 (4.9)	Not reported	36 (7.8)	Not reported
Diarrhoea	25 (5.3)	Not reported	17 (3.6)	Not reported	N/A	N/A	N/A	N/A
Back pain	24 (5.1)	Not reported	16 (3.4)	Not reported	N/A	N/A	N/A	N/A

	The BOREAS trial				The NOTUS trial			
Adverse events	**Dupilumab (N=469)**		**Placebo (N=470)**		**Dupilumab (N=469)**		**Placebo (N=464)**	
Accidental overdose	xxx	xxx	xxx	xxx	xxx	xxx	32 (6.9)	Not reported

Figure note: *A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

In the health economic model, AEs with a frequency of ≥5% in either the intervention group of the comparator group reported in Bhatt et al. 2023 were included. The clinical expert was consulted in terms of which of these AEs would typically require treatment, which were those included in the model. Typically, upper respiratory tract infections, headache and hypertension does not receive treatment at the hospital according to the clinical expert. Thus, these were not included in the health economic analysis. The included AEs are presented in Table 37.

Table 37 Adverse events used in the health economic model

Adverse events	Intervention	Comparator		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
Nasopharyngitis, n (%)	9.4%	9.6%	Bhatt et al. 2023	Included based on input from the clinical expert
COPD (exacerbation), n (%)	5.8%	6.0%	Bhatt et al. 2023	Included based on input from the clinical expert
Covid-19, n (%)	4.1%	5.7%	Bhatt et al. 2023	Included based on input from the clinical expert
Diarrhea, n (%)	5.3%	3.6%	Bhatt et al. 2023	Included based on input from the clinical expert
Back pain, n (%)	5.1%	3.4%	Bhatt et al. 2023	Included based on input from the clinical expert

Safety data from external literature applied in the health economic model
N/A as no external literature was applied to inform the health economic model.

Table 38 Adverse events that appear in more than X % of patients, N/A

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events

Adverse events	Intervention (N=x)	Comparator (N=x)	Difference, % (95 % CI)
Adverse event, n	N/A		

10. Documentation of health-related quality of life (HRQoL)

In the health economic model, utilities were derived based on EQ-5D-5L data from the NOTUS trial. In addition to the EQ-5D-5L results used for utilities in the model, HRQoL results measured with the SGRQ were also presented. EQ-5D-5L was presented in accordance with DMC guidelines. The rationale for also presenting HRQoL results from the SGRQ is that the SGRQ is a frequently used disease specific QoL assessment tool validated in COPD (61–63).

Table 39 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
The SGRQ	Pooled analysis of BOREAS and NOTUS	Assess the clinical effectiveness in terms of improving the HRQoL
EQ-5D-5L	NOTUS	Assess the clinical effectiveness in terms of improving the HRQoL and deriving utilities

10.1 Presentation of the health-related quality of life measured with the SGRQ

10.1.1 Study design and measuring instrument

COPD and its symptoms have a substantial impact on HRQoL. Worse lung function, exacerbations, and persistent respiratory symptoms, including more severe dyspnoea and severity of cough, are associated with worse patient-reported HRQoL and symptoms of anxiety, depression, and sleep disturbance. Thus, a priori it was expected that the HRQoL would increase due to the improvements in lung function and exacerbation rates observed with dupilumab treatment. The validity of the SGRQ questionnaire was discussed in section 3.7.1. The questionnaire consists of 76 items divided into three parts measuring symptoms, activity limitation and social and emotional impact of disease (64). Each item is accorded a weight determined by the degree of distress accorded to each symptom or state described. Overall scores range from 0 (no effect on quality of life) to a maximum score of 100 (maximum perceived distress); thus, a higher score means a poorer QoL and the questionnaire is suitable for administration in healthy people (65).

The change from baseline in SGRQ was reported as a LS mean difference measured with MMRM 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.

10.1.2 Data collection

SGRQ data was collected at baseline, week 4, week 12, week 24, week 36 and week 52. For the change from baseline in SGRQ, if the study intervention was discontinued prior to week 12 or week 52, all data collected after discontinuation were used in the analysis. For missing data imputation, missing data were imputed latently by MMRM based on missing at random. In terms of the proportion of SGRQ improvement (≥4 points) at week 52 for discontinuation of the study intervention prior to week 52, off-study intervention data were included in the analysis (treatment policy strategy). For missing data imputation, participants having missing data at week 52 or improvements <4 points were considered as non-responders.

Table 40 reports relevant data collection time points and missing observations for each time point and the number and percentage missing since randomisation. Characteristics of patients who have missing values was not available.

Table 40 Pattern of missing data and completion. Source: Sanofi data on file.

Time point	HRQoL population, N	Missing, N (%)	Expected to complete, N	Completion, N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	XXX	XXX	XXX	XXX
Week 4	XXX	XXX	XXX	XXX
Week 12	XXX	XXX	XXX	XXX
Week 24	XXX	XXX	XXX	XXX
Week 36	XXX	XXX	XXX	XXX
Week 52	XXX	XXX	XXX	XXX

Table note: Expected to complete was reported as the number of patients with data available at the time point X. Completion was reported as the number of patients with data available at baseline and time point X.

10.1.3 HRQoL results

10.1.3.1 Change from baseline in the SGRQ total score

In the ITT population, improvement from baseline in the SGRQ total score at week 52 was greater in the dupilumab group than in the placebo group: the LS mean change from baseline at week 52 was −9.945 (SE: 0.636) in the dupilumab group and −6.579 (SE: 0.640) in the placebo group. The LSM difference was −3.366 (95% CI: -4.953, -1.778, <.0001) (5). Patients reported improvement as early as week 4 in BOREAS and week 12 In the NOTUS trial. The result is illustrated in Figure 15 and the LS means at the different time points are presented in Table 41.

Figure 15: LSM change from baseline in the SGRQ from BOREAS (left) and NOTUS (right). Source: Sanofi data on file.

Figure note: LS: least squares, CI: confidence interval. Error bars represent 95% confidence intervals. 95% CIs have not been adjusted for multiplicity and should not be used for hypothesis testing.

Table 41 SGRQ summary statistics. Source: Sanofi data on file.

	Dupilumab		Placebo		Dupilumab vs. Placebo
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Week 4	XXX	XXX	XXX	XXX	XXX
Week 12	XXX	XXX	XXX	XXX	XXX
Week 24	XXX	XXX	XXX	XXX	XXX
Week 36	XXX	XXX	XXX	XXX	XXX
Week 52	XXX	XXX	XXX	XXX	XXX

Table note: Means are LS mean derived from MMRM model. N's are number of patients included in the model.

10.1.3.2 Proportion of patients with SGRQ score improvement from baseline ≥4 points at week 52

In the pooled analysis, the proportion of participants who achieved a clinically meaningful response in SGRQ total score at week 52 (i.e., improvement ≥4 points) was higher in the dupilumab group than in the placebo group: XXX versus XXX and the odds ratio was XXX, nominal p=0.0089. The treatment benefit of dupilumab was observed as early as week 4 (nominal p=0.0152) and was sustained over the 52-week intervention period.

10.2 Presentation of the health-related quality of life measured with EQ-5D-5L

10.2.1 Study design and measuring instrument

The EQ-5D-5L questionnaire is a standardised HRQoL questionnaire that consists of two parts: the ED-5D descriptive system and the EQ VAS. The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression); each with 5 dimensions ranging from "no problems" to "extreme problems". The digits for the 5 dimensions are combined into a 5-digit number describing the respondent's health state and is subsequently converted into a single index value by using EQ-5D-5L value sets based on the Danish tariffs from Jensen et al. 2021 (66), see section 10.4.4. The EQ VAS records the participant's self-rated health status on a vertical VAS and ranges from 0 (worst imaginable health status) to 100 (best imaginable health state) (67).

The change from baseline in EQ VAS score was reported as a LS mean difference measured with the MMRM model with the change from baseline in EQ-5D-5L index score up to week 52 as response variables, and treatment group, region (pooled country), ICS dose, smoking status at screening, visit, treatment-by-visit interaction, baseline EQ-5D-5L index score, and EQ-5D-5L index score baseline-by-visit interaction as covariates.

10.2.2 Data collection

In the NOTUS trial, EQ-5D-5L data was collected at baseline, week 24 and week 52. Table 42 presents data from the ITT population with the opportunity to reach week 52. For missing data imputation, missing data were imputed latently by MMRM based on missing at random assumption.

Table 42 Pattern of missing data and completion. Source: Sanofi data on file.

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is	Number of patients "at	Number of patients who completed (% of

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
		missing (% of patients at randomization)	risk" at time point X	patients expected to complete)
Baseline	Placebo: XXX Dupilumab: XXX	Placebo: XXX Dupilumab: XXX	Placebo: XXX Dupilumab: XXX	Placebo: XXX Dupilumab: XXX
Week 24	Placebo: 359 Dupilumab: 362	Placebo: 102 (28.4%) Dupilumab: 97 (26.8%)	Placebo: 257 Dupilumab: 265	Placebo: XXX Dupilumab: XXX
Week 52	Placebo: XXX Dupilumab: XXX	Placebo: XXX Dupilumab: XXX	Placebo: XXX Dupilumab: XXX	Placebo: XXX Dupilumab: XXX

10.2.3 HRQoL results

Table 43 provides the results in terms of change from baseline in EQ VAS score up to week 52 in the ITT population with the opportunity to reach week 52.

Table 43 HRQoL summary statistics, change from baseline in EQ-5D-5L single index score Danish tariffs from MMRM. Source: Sanofi data on file.

	Dupilumab		Placebo		Dupilumab vs. Placebo
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	XXX	XXX	XXX	XXX	XXX
Week 24	XXX	XXX	XXX	XXX	XXX
Week 52	XXX	XXX	XXX	XXX	XXX

Table note: Means are LS means. N's are number of participants in the model.

10.3 Health state utility values (HSUVs) used in the health economic model

To demonstrate the potential impact of treatment on patient's quality of life, the health economic model accounts for the following:

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

10.3.1 HSUV calculation

In BOREAS trial, EQ-5D-5L was only collected at baseline but in the NOTUS trial EQ-5D-5L was collected at baseline and during follow-up at week 24 and week 52. In addition, in both trials HRQoL was evaluated through the SGRQ at baseline and during follow-up (at week 4, week 12, week 24, week 36 and week 52, and the SGRQ can be mapped to EQ-5D via published algorithms such as Starkie et al. 2011 (68). However, this mapping was not providing a good fit to the baseline EQ-5D-5L data from BOREAS and NOTUS and thus not used in the current application. Instead, NOTUS EQ-5D-5L was applied, which is also in accordance with DMC methods.

Table 44 presents the parameters included in the calculation of HSUV based on the Danish preference-weights from the general Danish population. All data collected during the on-treatment period (from first IMP to end of treatment or last IMP + 16 days) were included. Missing GOLD were imputed as per Markov SAP and no imputation of missing utility was performed.

Table 44 Parameters included in the HSUV estimates. Source: Sanofi data on file

	Class or unit	Estimate (SE)	95% CI	P value
Intercept		XXX	XXX	XXX
Age	1 year	XXX	XXX	XXX
Gender, Male	Male (ref: Female)	XXX	XXX	XXX
Single index score at baseline, 1 point	1 point	XXX	XXX	XXX
Health State - GOLD status				
Moderate FEV1 (ref: Mild FEV1)		XXX	XXX	XXX
Severe FEV1 (ref: Mild FEV1)		XXX	XXX	XXX
Very Severe FEV1 (ref: Mild FEV1)		XXX	XXX	XXX

Table 45 presents the utilities based on the Danish preference-weights according to GOLD severity at the same visit during on-treatment period from the ITT population with an opportunity to reach week 52. No imputation of missing GOLD was performed.

Table 45 Utility measurements per COPD state. Source: Sanofi data on file.

COPD stage	Dupilumab (N=865)	Placebo (N=850)	All (N=1,715)
GOLD Grade 1			
Number	XXX	XXX	XXX
Mean (SD)	XXX	XXX	XXX
GOLD Grade 2			
Number	XXX	XXX	XXX
Mean (SD)	XXX	XXX	XXX
GOLD Grade 3			
Number	XXX	XXX	XXX
Mean (SD)	XXX	XXX	XXX
GOLD Grade 4			
Number	XXX	XXX	XXX
Mean (SD)	XXX	XXX	XXX

Abbreviation: COPD = chronic obstructive pulmonary disease; LS = least square

10.3.1.1 Mapping

No mapping has been applied.

10.3.2 Disutility calculation

10.3.2.1 Disutility associated with exacerbation

Since exacerbation events have a profound impact on COPD's clinical prognosis, a disutility was applied to each exacerbation event. Based on the evidence from Jackson et al. (69), exacerbations are associated with deteriorating health and HRQoL during and after events. Hence, an acute disutility was applied during the exacerbation event followed by a chronic disutility for a period of 1-year following exacerbation. The acute exacerbation disutility was assumed to last for a duration of one month. In addition to Jackson et al. (69), the model also has the flexibility to use the acute disutilities derived directly from the NOTUS trial. In the NOTUS trial, utility regression, exacerbations within 3 months prior the utility assessment were included as acute event. The disutilities are summarized in Table 46.

Table 46 Summary of disutilities associated with exacerbation

Exacerbation	Acute Impact		Chronic Impact		Source
	Utility Decrement	Duration (Months)	Utility Decrement	Duration (Months)	

Moderate exacerbation	0.05	1	0.01	12	Jackson et al. (69)
Severe exacerbation	0.09	1	0.02	12	
Moderate exacerbation	XXX	XXX	XXX	XXX	NOTUS, Sanofi data on file
Severe exacerbation	XXX	XXX	XXX	XXX	

10.3.2.2 Disutility associated with AEs

The model has the flexibility to account for disutilities associated with AEs. If this is included, the associated disutility and duration will be applied to the proportion of patients who experienced the event every cycle. Since the adverse events considered in the model were mild, the disutilities associated with adverse events were assumed to be 0 in the base case.

10.3.3 HSUV results

The utilities shown in Table 47 were used in the model to calculate QALYs to reflect the HRQoL experienced by patients in the various COPD and exacerbation health states in the model. The applied utilities were age-adjusted to account for the decrease in HRQoL related to increasing age in accordance with DMC methods.

Table 47 Overview of health state utility values and disutilities

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Mild COPD	XXX	EQ-5D-5L	DK	Estimate is based on mean from the NOTUS trial.
Moderate COPD	XXX	EQ-5D-5L	DK	Estimate is based on mean from the NOTUS trial.
Severe COPD	XXX	EQ-5D-5L	DK	Estimate is based on mean from the NOTUS trial.
Very severe COPD	XXX	EQ-5D-5L	DK	Estimate is based on mean from the NOTUS trial.
Disutilities associated with exacerbation				
Moderate exacerbation - Acute	0.053	N/A	N/A	Derived from Jackson et al. (69)
Severe exacerbation - Acute	0.087	N/A	N/A	Derived from Jackson et al. (69)
Moderate exacerbation - Chronic	0.013	N/A	N/A	Derived from Jackson et al. (69)
Severe exacerbation - Chronic	0.021	N/A	N/A	Derived from Jackson et al. (69)

10.4 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

Not applicable.

10.4.1 Study design

Not applicable.

10.4.2 Data collection

Not applicable.

10.4.3 HRQoL Results

Not applicable.

10.4.4 HSUV and disutility results

Not applicable.

Table 48 Overview of health state utility values [and disutilities], N/A

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
HSUV A	N/A			

Table 49 Overview of literature-based health state utility values, N/A

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUV A				
Study 1	N/A			

11. Resource use and associated costs

All costs related to treating patients with moderate to severe COPD with type-2 inflammation with dupilumab and background therapy were included in the health economic model. To estimate the resource use and identify unit costs, the SmPC on dupilumab, data from the BOREAS and NOTUS trials, input from the Danish clinical

expert and assumptions were applied. In the following, descriptions of each cost element and how the element was valued in the health economic analysis are presented.

11.1 Medicine costs - intervention and comparator

The medicines included in the model were dupilumab and background therapy with LAMA/LABA/ICS. The PPP on the package with dupilumab and LABA/LAMA/ICS included in the model is presented in Table 51.

Table 50 Medicine costs used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Dupilumab	300 mg	Not included	Every other week	Not included
Trelegy Ellipta	92+55+22 micrograms	Not included	Once daily	Not included

Table 51 Package information on medicines included in the model. Source: Medicinpriser.dk (25 November 2024)

Medicine	Strength	Package size	Pharmacy purchase price [DKK]
Dupilumab (Dupixent®)	300 mg	2 pre-filled syringes	8,274.34
Trelegy Ellipta "GlaxoSmithKline Pharma"	92+55+22 micrograms	3 x 30 doses of powder for inhalation	1,100

11.2 Medicine costs – co-administration

Not applicable.

11.3 Administration costs

Dupilumab is administered by subcutaneous injections. Based on the SmPC on dupilumab, a patient may self-inject dupilumab or the patient's caregiver may administer dupilumab after proper training in injection technique has been provided (70). Based on this, it was assumed that the first injection of dupilumab was administered at the hospital where patients in addition to the first injection received training in injection technique. The rest of the injects were assumed to be administered at home by the patient. An outpatient visit was applied to account for the visit to the hospital for the first injection and training, please see Table 52. No addition administration cost for background therapy was included as this can be administered orally at home.

Table 52 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Subcutaneous injections of dupilumab	Once	1,989	17MA98	DRG 2024

11.4 Disease management costs

- Resource utilisation was assumed to vary for patients separately for COPD stage as well as exacerbation. The clinical expert was consulted in terms of estimating the resource use and the frequency of resources based on an analysis from Fenwick et al. 2021 (8) that assessed the cost-effectiveness of fluticasone furoate/umeclidinium/vilanterol versus budesonide/formoterol for treating COPD from a UK National Health Service perspective. The resource use and frequencies from the trial were validated by the Danish clinical expert to make sure that the resource use reflected Danish clinical practise. Table 53 presents the resource use and the frequency of resources associated with the treatment necessitated by the patient's COPD stage. Table 53 presents the resource use and the frequency of resources related to exacerbations. The applied unit costs are presented in

Table 54.

Table 53 Frequency of resources related to disease management included in the model

Resources	Annual frequency			
	Mild COPD	**Moderate COPD**	**Severe COPD**	**Very Severe COPD**

Outpatient visit, respiratory physician	0	1	2	3
GP visit	1	2	2	2
Spirometry	1	2	3	3
Influenza vaccination	0.75	0.75	0.75	0.75
Pneumococcal vaccination	0	0.15	0.30	0.30
Oxygen therapy (days)	0	0	35	35
ICU days	0	0	2	2
Inpatient, non-ICU days	0.25	1	2	2
ER visits*	0	0	0	0
Visit other healthcare provider	1	2	3	3
Readmissions	0.025	0.05	0.2	0.2
Emergency ambulance transfer	0	0	0	0
Emergency nurse	0	0	0	0

Note: The annual frequencies were obtained from Fenwick et al. 2021 and validated by the Danish clinical expert. For clarification, e.g., 0.75 annual influenza vaccinations should be interpreted as 75% of patients having an annual influenza vaccination. *ER vistis were assumed to be associated with exacerbations and thus not accounted for here also to avoid double-counting.

Table 54 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Outpatient visit, respiratory physician	Please see Table 53 and Table 53	1,989	17MA98	DRG 2024
GP visit	Please see Table 53 and Table 53	161	0101	2024 fees (71)
Spirometry	Please see Table 53 and Table 53	429	0101 and7121	2024 fees (71)
Influenza vaccination	Please see Table 53 and Table 53	160	8940	2024 fees (71)

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Pneumococcal vaccination	Please see Table 53 and Table 53	160	8940	2024 fees (71)
Oxygen therapy	Please see Table 53 and Table 53	68.45	N/A	Daily average of the per year cost of oxygen therapy, Danish Nurses' Organization (72)
ICU admission, per day	Please see Table 53 and Table 53	2,837	04MA11	DRG 2024, daily cost per admission derived using DRG tariff and trim point*
Inpatient, non-ICU admission	Please see Table 53 and Table 53	2,837	04MA11	DRG 2024, daily cost per admission derived using DRG tariff and trim point
ER visits	Please see Table 53 and Table 53	1,989	17MA98	DRG 2024
Visit other health care providers	Please see Table 53 and Table 53	161	0101	2024 fees (71)
Readmissions	Please see Table 53 and Table 53	31,211	04MA12	DRG 2024, combination of DJ441 and ZZ0202B
Emergency ambulance transfer	Please see Table 53 and Table 53	1,729	N/A	Cost derived from Copenhagen Economics (73) and inflated to 2024-prices.
Emergency nurse	Please see Table 53 and Table 53	462	N/A	2024 fee (74)

*In interactive DRG, the same DRG tariff is generated when selecting that the admission is acute and planned, thus, the same DRG tariff was used for ICU admissions and non-ICU admissions.

The model also included costs related to managing exacerbations. The resource use related to managing moderate and severe exacerbations is presented in Table 55. The resource use related to managing exacerbations was validated by the clinical expert.

When applying the unit costs presented in

Table 54 and the exacerbation frequencies in Table 55, a unit cost of DKK 1,622 and DKK 43,381 for a moderate exacerbation and a severe exacerbation were estimated, respectively.

Table 55 Exacerbation frequencies used in the model

Activity	Frequency per moderate exacerbation	Frequency per severe exacerbation
Outpatient visit, respiratory physician	0.34	0.82
GP visit	0.66	0.7
Spirometry	0	0
Influenza vaccination	0	0
Pneumococcal vaccination	0	0
Oxygen therapy	0	0.21
ICU admission, days	0	0.86
Inpatient, non-ICU admission	0	11.08
ER visits	0	0.25
Visit other health care providers	0.27	0.5
Readmissions	0	0.162
Emergency ambulance transfer	0.3	0.9
Emergency nurse	0.6	1.2

11.5 Costs associated with management of adverse events

The adverse events relevant to include in the health economic model were discussed with the clinical expert. The frequencies of the adverse were presented in section 9 along with the rationale for including the adverse events presented in Table 56.

According to the clinical expert, most adverse events reported in the BOREAS and NOTUS trials can be managed with an additional GP visit, expect COPD exacerbations, which would be managed as exacerbations are currently managed in the model i.e., with hospitalization. The unit cost for a GP visit was derived from the DMC unit cost catalogue and the unit cost for a hospitalization for a COPD exacerbation was based on the DRG 2024 code 04MA12.

Table 56 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
Nasopharyngitis	0101	160.72
COPD (exacerbation)	04MA12	2,837 (04MA12 divided by the trim point of 11 days)
Covid-19	0101	160.72
Diarrhea	0101	160.72
Back pain	0101	160.72

11.6 Subsequent treatment costs

No subsequent treatments were included in the model. The rationale for not including subsequent treatment was that at the time of preparing the current application, no treatments have been approved for use after triple therapy with LABA/LAMA/ICS. When patients discontinue dupilumab treatment in the model, they continue receiving background therapy. In addition, no discontinuation in the background therapy arm was included.

Table 57 Medicine costs of subsequent treatments, N/A

Medicine	Strength	Package size	Pharmacy purchase price [DKK]	Relative dose intensity	Average duration of treatment
[Name of subsequent treatment]	N/A	N/A	N/A	N/A	N/A
		N/A	N/A	N/A	N/A
[Name of subsequent treatment]	N/A	N/A	N/A	N/A	N/A
	N/A	N/A	N/A	N/A	N/A

11.7 Patient costs

In accordance with DMC guidelines, patient-related time use and costs and transportation costs were included in the model. No caregiver time or costs were included in the model. The patient time associated with dupilumab and background therapy treatment was based on the time spent on treatment-related activities and traveling to and from the hospital. Based on the DMC guideline, a cost of DKK 203 per patient hour was applied.

In terms of transportation, a distance of 20 km to and from the hospital (40 km in total per visit) was assumed, and a unit cost per km of DKK 3.73 was applied in accordance with DMC guidelines. Thus, a transportation cost of DKK 149 was applied for each hospital visit. It was assumed that patients spend 30 minutes on transportation to and from the hospital i.e., 60 minutes per visit.

The activities to which patient time use and transportation were ascribed, and the time spent by the patient on each activity including one hour of transportation, are presented in Table 58. The patient time spent on each activity and managing each included AEs was derived based on input from the clinical expert. Each activity was ascribed a transportation cost of DKK 149.

Table 58 Patient costs used in the model

Activity	Time spent [minutes or hours]*
Subcutaneous injection and training in injection technique	2 hours
Outpatient visit to respiratory physician	1.5 hours
GP visit	1.5 hours
Spirometry	1.25 hours
Influenza and pneumococcal vaccination	1.5 hours
Oxygen therapy	1.5 hours
ICU day	24 hours per day
Inpatient day, non-ICU	24 hours per day
ER visit	6 hours
Visit other health care provider	1.5 hours
Pneumococcal vaccination	1.5 hours
Readmissions	24 hours per day
Emergency ambulance transfer	1 hour per day
Emergency nurse	1 hour per day
Managing Nasopharyngitis	1.25 hours
Managing back pain	1.25 hours
Managing COPD exacerbation	24 hours per day
Managing diarrhea	1.50 hours
Managing COVID-19	1.25 hours

*Please note that the patient time presented in the table is inclusive one hour of transportation time.

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

No other costs were included.

12. Results

12.1 Base case overview

Table 59 provides an overview of the settings applied in the base case of the health economic analysis.

Table 59 Base case overview

Feature	Description
Comparator	Background therapy comprising triple-therapy with ICS/LABA/LAMA
Type of model	Markov model
Time horizon	Until the patients reach 100 years
Treatment line	As an add-on to triple therapy with ICS/LABA/LAMA
Measurement and valuation of health effects	EQ-5D-5L from the NOTUS trial and Danish preference weights
Costs included	Medicine costs Administration costs Disease management costs Costs associated with managing AEs Patient and transportation costs
Dosage of medicine	Dupilumab: Patients received 300 mg subcutaneous dupilumab once every second week. Background therapy: One inhalation per day with 92 micrograms fluticasone furoate, 65 micrograms umeclidinium bromide equivalent to 55 micrograms umeclidinium and 22 micrograms vilanterol (as trifenatate).
Average time on treatment	Dupilumab: 4.74 years Background therapy: 4.20 years
Parametric function for PFS	N/A
Parametric function for OS	N/A
Inclusion of waste	Not included
Average time in model health state	Dupilumab
Mild COPD	Mild: 0 months
Moderate COPD	Moderate: 31.7 months
Severe COPD	Severe: 21.4 months
Very severe COPD	Very severe: 3.7 months

Feature	Description
	Background therapy Mild: 0 months Moderate: 26.9 months Severe: 18.4 months Very severe: 5.1 months

12.1.1 Base case results

In the base case, the incremental cost and incremental QALY per patient for dupilumab compared to background therapy was DKK 314.925and 0,54, respectively, over a lifelong time horizon. Table 60 presents an overview of the base case results.

Table 60 Base case results, discounted estimates

	Dupilumab	Background therapy	Difference
Medicine costs	XXX	XXX	XXX
Medicine costs – co-administration	N/A	N/A	N/A
Administration	XXX	XXX	XXX
Disease management costs	XXX	XXX	XXX
Costs associated with management of adverse events	XXX	XXX	XXX
Subsequent treatment costs	XXX	XXX	XXX
Patient costs	XXX	XXX	XXX
Palliative care costs	N/A	N/A	N/A
Total costs	XXX	XXX	289,542
Life years gained (Mild COPD)	0	0	0
Life years gained (Moderate COPD)	2.3	2.0	0.3
Life years gained (Severe COPD)	1.6	1.4	0.2
Life years gained (Very severe COPD)	0.3	0.4	-0.1
Total life years	4.2	3.8	0.4

	Dupilumab	Background therapy	Difference
QALYs (Mild COPD)	0	0	0
QALYs (Moderate COPD)	1.9	1.7	0.3
QALYs (Severe COPD)	1.3	1.1	0.2
QALYs (Very severe COPD)	0.2	0.3	-0.1
QALYs (adverse reactions)	N/A	N/A	N/A
Total QALYs	3.4	3.0	0.4
Incremental costs per life year gained	xxxxxx **DKK**		
Incremental cost per QALY gained (ICER)	xxxxxx **DKK**		

12.2 Sensitivity analyses

Uncertainty in the input parameters in the model has been explored through DSAs and a PSA and scenario analyses which are presented in this section.

12.2.1 Deterministic sensitivity analyses

The DSAs included in the present application are presented in Table 61. Sensitivity was assessed by varying the input parameters of the model by selecting the 2.5th percentile to represent the lower bound and the 97.5th percentile to represent the upper bound.

Table 61 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	-	-	xxxxxx	xxx	xxxxxx
ExaRisk AllTrial: Severe exa - Severe COPD	2.5th percentile	To assess the impact of this parameter	xxxxxx	xxx	xxxxxx
	97.5th percentile	To assess the impact of this parameter	xxxxxx	xxx	xxxxxxx
ExaRisk AllTrial: Severe exa - Moderate COPD	2.5th percentile	To assess the impact of this parameter	xxxxxx	xxx	xxxxxx
	97.5th percentile	To assess the impact of this parameter	xxxxxx	xxx	xxxxxxx

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Mortality adjustment factor	2.5th percentile	To assess the impact of this parameter	xxxxxx	xxx	xxxxxx
	97.5th percentile	To assess the impact of this parameter	xxxxxx	xxx	xxxxxx
% end of amelioration Dupi: Moderate COPD	2.5th percentile	To assess the impact of this parameter	xxxxxx	xxx	xxxxxx
	97.5th percentile	To assess the impact of this parameter	xxxxxx	xxx	xxxxxx
ExaRisk Baseline: Moderate exa - Moderate	2.5th percentile	To assess the impact of this parameter	xxxxxx	xxx	xxxxxx
	97.5th percentile	To assess the impact of this parameter	xxxxxx	xxx	xxxxxx
% end of amelioration Dupi: Severe COPDCOPD	2.5th percentile	To assess the impact of this parameter	xxxxxx	xxx	xxxxxx
	97.5th percentile	To assess the impact of this parameter	xxxxxx	xxx	xxxxxx
% end of amelioration SOC: Moderate COPD	2.5th percentile	To assess the impact of this parameter	xxxxxx	xxx	xxxxxx
	97.5th percentile	To assess the impact of this parameter	xxxxxx	xxx	xxxxxx
Utility: Moderate COPD	2.5th percentile	To assess the impact of this parameter	xxxxxx	xxx	xxxxxx
	97.5th percentile	To assess the impact of this parameter	xxxxxx	xxx	xxxxxx
ExaRisk Baseline: Moderate exa - Severe COPD	2.5th percentile	To assess the impact of this parameter	xxxxxx	xxx	xxxxxx
	97.5th percentile	To assess the impact of this parameter	xxxxxx	xxx	xxxxxx
ExaRisk AllTrial: Moderate exa - Severe COPD	2.5th percentile	To assess the impact of this parameter	xxxxxx	xxx	xxxxxx
	97.5th percentile	To assess the impact of this parameter	xxxxxx	xxx	xxxxxx

The results were most sensitive to changes to the mortality adjustment factor that was used to align model mortality with the relevant Danish population and to the patient distributions related the different COPD stages in the model at the end of the

amelioration phase. Figure 16 illustrates the tornado diagram containing the results of the DSA.

Figure 16: One-way sensitivity analysis results for dupilumab compared to background therapy

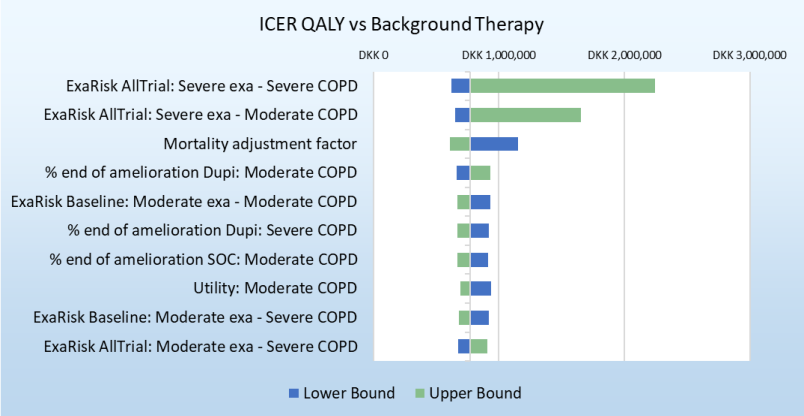


Table 62 presents the incremental cost, incremental QALYs and the associated Incremental cost-effectiveness ratio (ICER) for four scenario analyses. In addition to changing the time horizon of the model, we present the results from a scenario analysis, where we have applied the same standardized mortality rate for the severe COPD stage and the very severe COPD stage.

It is observed that the ICER decreases as the model's time horizon extends. The decreasing ICER reflects the long-term effectiveness of those individuals who experience a prolonged and positive response to dupilumab. For this reason, we also believe that the most accurate representation is obtained with a lifelong time horizon, as assumed in the model's base case.

Table 62 Scenario analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	-	-	xxxxxx	xxx	xxxxxx
Time horizon of 1 year	Reducing the time horizon to 1 year	In accordance with DMC guidelines	xxxxxx	xxx	xxxxxx
Time horizon of 5 years	Reducing the time horizon to 5 years	In accordance with DMC guidelines	xxxxxx	xxx	xxxxxx
Time horizon of 10 years	Reducing the time horizon to 10 years	In accordance with DMC guidelines	xxxxxx	xxx	xxxxxx

12.2.2 Probabilistic sensitivity analyses

To assess the uncertainty surrounding the variables included in the model, a PSA was performed using 1,000 iterations. The PSA evaluated the result of the health economics analysis when several parameters of the models were varied simultaneously. Figure 17 presents the cost-effectiveness acceptability curves (CEAC) that illustrates the cost-effectiveness probability at different willingness-to-pay thresholds. Figure 18 presents the scatter plot from the PSA. As seen, 995 of the simulated ICERs from the PSA are located in the north-east quadrant, where dupilumab is more effective and more costly compared to background therapy. 5 of the simulated ICERs from the PSA are located in the north-west quadrant, where dupilumab is less effective and more costly compared to background therapy. Figure 19 presents a convergence plot of the estimated ICER mean as a function of the number of PSA simulations.

Figure 20 presents the impact of the PPP of dupilumab on the estimated ICER value.

Figure 17: Cost-effectiveness acceptability curves

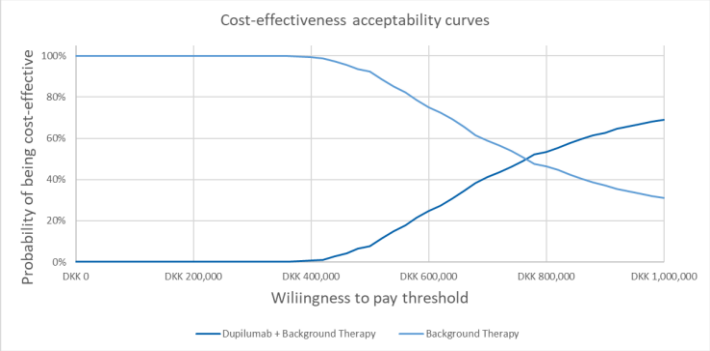


Figure 18: Scatter plot from PSA

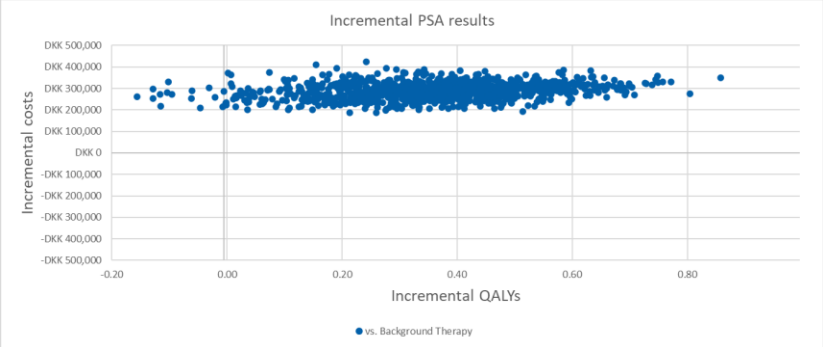


Figure 19: Convergence plot for the estimated mean

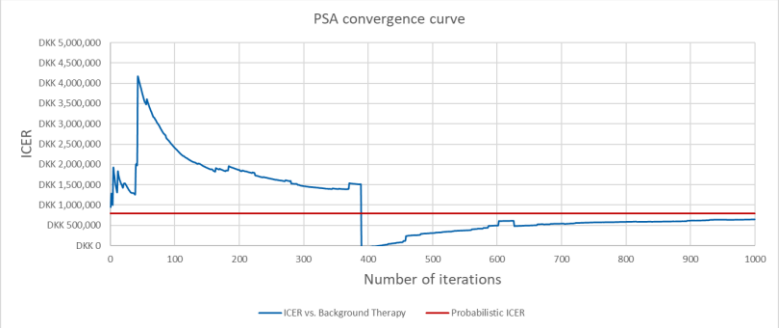
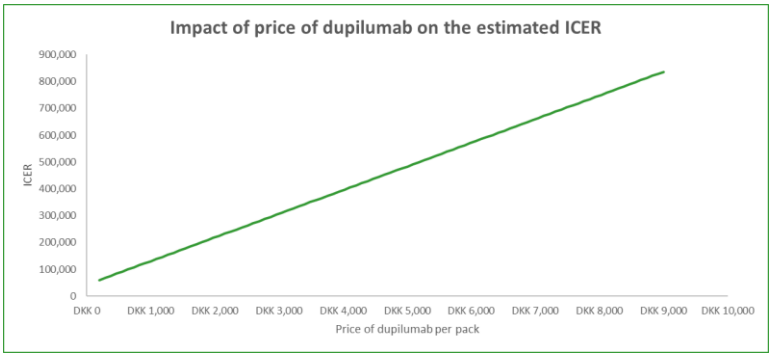


Figure 20: Impact of PPP of dupilumab on the estimated ICER



13. Budget impact analysis

The purpose of the budget impact analysis was to estimate the budgetary impact of recommending dupilumab as standard treatment for patients with moderate to severe COPD with type-2 inflammation. The budget impact was estimated per year in the first 5 years after the recommendation of dupilumab. The budget impact analysis compares the expenditures in the scenario where dupilumab is recommended as a possible standard treatment and the scenario where dupilumab is not recommended as a possible standard treatment. The total budget impact per year is the difference between the two scenarios. The cost results for year 1-5 (not discounted and excluding patient and transportation costs) from the cost-utility analysis informed the budget impact analysis.

Number of patients (including assumptions of market share)

The number of patients in the budget impact model was informed by DrKOL data (see section 3.2). According to these data, xxx patients meet the criteria for treatment with dupilumab. However, due to the patients' age, fragility, and adherence to current therapy it is estimated that only 50% of these patients (corresponding to xxx patients) will be initiated on treatment with dupilumab. Thus, the market share for dupilumab, given recommendation, has been set to 50% in the model.

For year 2-5, new patients will meet the criteria for treatment with dupilumab and for these patients it is assessed that 203 patients yearly will be initiated on treatment with dupilumab. Mortality in the subsequent years (year 2-5, year 3-5 etc.) of the patients on

treatment with dupilumab or background therapy is accounted for in the cost estimates for these years.

Table 63 Number of new patients expected to be treated over the next five-year period if dupilumab is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Dupilumab	xxx	xxx	xxx	xxx	xxx
Background therapy	xxx	xxx	xxx	xxx	xxx
			Non-recommendation		
Dupilumab	x	x	x	x	x
Background therapy	xxx	xxx	xxx	xxx	xxx

To assess the impact of the mortality rates implied by the Markov model on the population sizes in the budget impact analysis with and without the recommendation of dupilumab, the yearly population sizes are presented in Table 64 using the prevalent and incident patient populations combined with the model-predicted yearly mortality rates.

Table 64 Projected patient populations over five years adjusted for mortality rates

	Year 1	Year 2	Year 3	Year 4	Year 5
With recommendation	xxx	xxx	xxx	xxx	xxx
Without recommendation	xxx	xxx	xxx	xxx	xxx

Budget impact

An overview of the results of the budget impact analysis is presented in Table 65. Based on the settings applied in the base and the PPP on dupilumab and SoC, the budget impact was estimated to DKK 190,071,337 over all 5 years in the budget impact analysis.

Table 65 Expected budget impact of recommending dupilumab for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
Dupilumab is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

14. List of experts

The consulted clinical expert was Anders Løkke Ottesen who is a clinical professor at the research department for medical diseases at Sygehus Lillebælt.

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Appendix A. Main characteristics of studies included

Table 66 Main characteristic of BOREAS

Trial name: BOREAS	**NCT number: NCT03930732**
Objective	The purpose of the BOREAS trial was to investigate the efficacy, safety, and tolerability of dupilumab administered every 2 weeks among patients with moderate-to-severe type 2 inflammatory COPD (5,47).
Publications – title, author, journal, year	Bhatt et al. 2023: 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. (5)
Study type and design	The BOREAS trial was a phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group study. After a 4-week (±1 week) screening period, patients who met the eligibility criteria underwent randomization in a 1:1 ratio to receive subcutaneous dupilumab (300 mg) or placebo every 2 weeks in a 52 weeks (±3 days) treatment period. Randomisation was stratified according to country and inhaled glucocorticoid dose at baseline. Patients entered a 12-week (±5 days) follow-up safety period after the treatment period where the patients no longer received dupilumab or placebo (5,47).
Sample size (n)	2,599 patients were screened for eligibility and a total of 939 patients underwent randomisation: 468 to the dupilumab group and 471 to the placebo group.
Main inclusion criteria	**Inclusion criteria** (75)**:** • Participants with a physician diagnosis of COPD who meet the following criteria at screening: o Current or former smokers with a smoking history of ≥10 pack-years. o Moderate-to-severe COPD (post-bronchodilator FEV_1/ FVC ratio <0.70 and post-bronchodilator FEV_1 % predicted >30% and ≤70%). o Medical Research Council (MRC) Dyspnea Scale grade ≥2. o 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. o Documented history of high exacerbation risk defined as exacerbation history of ≥2 moderate or ≥1 severe within the year prior to inclusion. At least

Trial name: BOREAS	NCT number: NCT03930732
	one exacerbation should have occurred while the patient was taking ICS/LABA/LAMA (or LABA/LAMA if ICS is contraindicated). Moderate exacerbations are recorded by the investigator and defined as acute exacerbation of COPD (AECOPD) that require either systemic corticosteroids (intramuscular, intravenous, or oral) and/or antibiotics. One of the two required moderate exacerbations has to require the use of systemic corticosteroids. Severe exacerbations are recorded by the investigator and defined as AECOPD requiring hospitalization or observation >24 hours in emergency department/urgent care facility. ○ Background triple therapy (ICS + LABA + LAMA) for 3 months prior to randomization with a stable dose of medication for ≥1 month prior to Visit 1; Double therapy (LABA + LAMA) allowed if ICS is contraindicated. • Evidence of Type 2 inflammation: Patients with blood eosinophils ≥300 cells/microliter at Visit 1.
Main exclusion criteria	**Exclusion criteria** (75)**:** • COPD diagnosis for less than 12 months prior to randomization. • A current diagnosis of asthma or history of asthma according to the 2018 Global Initiative for Asthma (GINA) guidelines or other accepted guidelines. • Significant pulmonary disease other than COPD (e.g., lung fibrosis, sarcoidosis, interstitial lung disease, pulmonary hypertension, bronchiectasis, Churg-Strauss Syndrome etc) or another diagnosed pulmonary or systemic disease associated with elevated peripheral eosinophil counts. • Cor pulmonale, evidence of right cardiac failure. • Treatment with oxygen of more than 12 hours per day. • Hypercapnia requiring Bi-level ventilation. • AECOPD as defined in inclusion criteria within 4 weeks prior to screening, or during the screening period. • Respiratory tract infection within 4 weeks prior to screening, or during the screening period. • History of, or planned pneumonectomy or lung volume reduction surgery. Patients who are participating in the acute phase of a pulmonary rehabilitation program, i.e., who started rehabilitation <4 weeks prior to screening (Note:

Trial name: BOREAS	NCT number: NCT03930732
	patients in the maintenance phase of a rehabilitation program can be included). • Diagnosis of α-1 anti-trypsin deficiency.
Intervention	The dupilumab group received 300 mg dupilumab subcutaneously administered once every 2 weeks (5).
Comparator(s)	The placebo group received 300 mg matching placebo administered once every 2 weeks (5).
Follow-up time	52 weeks treatment period and 12 weeks of follow-up (64 weeks in total).
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Primary efficacy endpoints** • Annualized rate of moderate-or-severe COPD exacerbations over the 52-week treatment period compared to placebo. Moderate exacerbations were defined as exacerbations that resulted in treatment with a systemic glucocorticoid, an antibiotic agent, or both. Severe exacerbations were defined as exacerbations that led to hospitalisation or an emergency medical care visit or that resulted in death (5,75). **Key secondary efficacy endpoints** (47) • Change in pre-bronchodilator FEV_1 from baseline to week 12 compared to placebo • Change in pre-bronchodilator FEV_1 from baseline to week 52 compared to placebo • Change from baseline to week 52 in the SGRQ total score compared to placebo • Proportion of patients with SGRQ score improvement from baseline ≥4 points at week 52 **Other secondary efficacy endpoints** (47) • Change in pre-bronchodilator FEV_1 from baseline through weeks other than 12 and 52 (i.e., weeks 2, 4, 8, 24, 36, and 44) • Change in post-bronchodilator FEV_1 from baseline to weeks 2, 4, 8, 12, 24, 36 and 52

Trial name: BOREAS	NCT number: NCT03930732
	• Change in forced expiratory flow (FEF) $_{25-75\%}$ from baseline to weeks 2, 4, 8, 12, 24, 36, 44, and 52 • Annualized rate of severe COPD exacerbations compared to placebo over the 52-week treatment period • Time-to-first moderate or severe COPD exacerbation compared with placebo during the 52- week treatment period using a Cox regression model. **Safety endpoints** (5,75) • Number of AEs/TEAEs • Percentage of patients with at least one incidence of potentially clinically significant abnormality (PCSA) in laboratory tests • Incidence of anti-drug antibodies against dupilumab **Selected exploratory endpoints** (47) • Change from baseline to week 52 in E-RS: COPD total score • Annualized rate of COPD exacerbations assessed by the EXACT tool • Change in FVC from baseline to weeks 2, 4, 8, 12, 24, 36 and Week 52 • Annualised loss of lung function as assessed by a FEV_1 slope analysis • Genetic analyses
Method of analysis	Efficacy was evaluated in the intention-to-treat population, which included all patients who underwent randomisation, and was analysed according to the trial group to which each patient was randomly assigned. Safety was evaluated in the safety population, which included all patients who received at least one full or partial dose of dupilumab or placebo, and was analysed according to the treatment each patient received. We estimated that a sample of 924 patients (462 in each trial group) would provide the trial with 90% power to detect a between-group difference in the annualized rate of moderate or severe exacerbations of 25% at week 52 at a two-sided alpha level of 0.049 (with an administrative penalty of 0.001 taken from the final analysis owing to a planned interim analysis). The primary endpoint was analysed with the use of a negative binomial model, with the total number of events occurring during the 52-week trial period as the response variable. The trial group, geographic region (pooled according to country), dose of inhaled glucocorticoid at baseline, smoking status at screening, physician-assessed disease severity at baseline, and number of moderate or severe exacerbation events of COPD within 1 year before trial enrollment were used as covariates, and the natural log of the duration of receipt of dupilumab or placebo was used as an offset variable. The key secondary endpoints

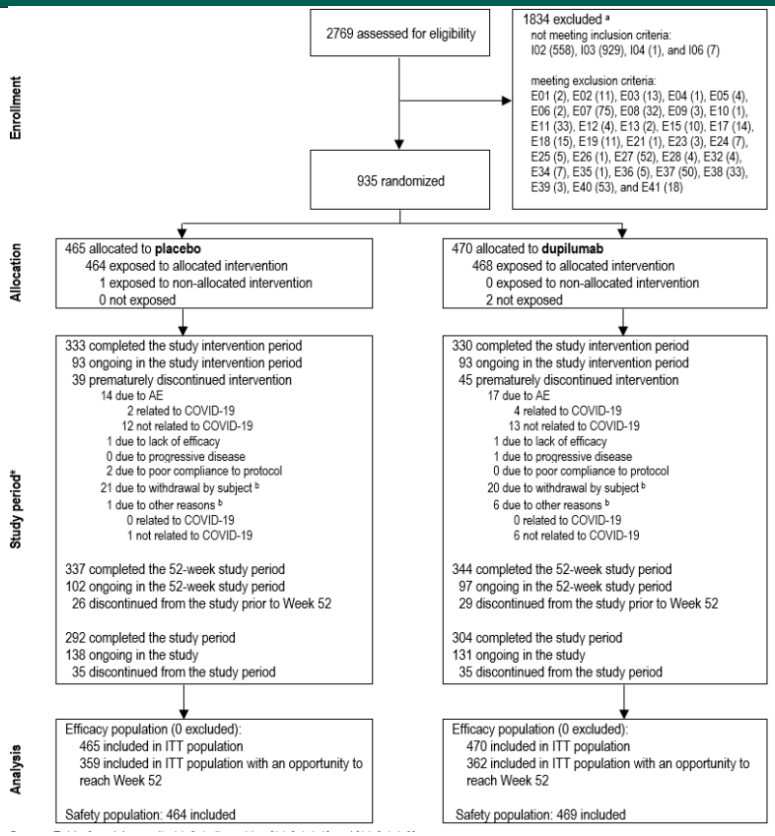
Trial name: BOREAS	NCT number: NCT03930732
	(i.e., the change from baseline in the prebronchodilator FEV1 at weeks 12 and 52, the change from baseline to week 52 in the SGRQ total score, and the percentage of patients with a change of at least 4 points in the SGRQ total score at week 52) were assessed with the use of a mixed-effects model for repeated measures that included the trial group, geographic region (pooled according to country), dose of inhaled glucocorticoid at baseline, smoking status at screening, visit, trial group–by–visit interaction, baseline value, baseline value–by–visit interaction, and other model-specific factors as covariates. A hierarchical testing procedure was used.
Subgroup analyses	In the BOREAS trial, the change from baseline in pre-bronchodilator FEV_1 at week 12 and the annual rate of moderate or severe COPD exacerbations during the 52-week treatment period were analysed in subgroups based on the following covariates: • Age group (<65, ≥65) • Gender (male, female) • Race (white, non-white) • Ethnicity (Hispanic or Latino, not Hispanic or Latino) • Region (Asia, Latin America, East Europe, Western Countries) • Territory (North America, European Union, Rest of world) • Baseline weight (Kg) (<70, ≥70-<90, ≥90) • Baseline weight (Kg) (<60, ≥60) • Baseline BMI (<25, ≥25-30, ≥30) • ICS dose level at baseline (High-dose ICS, non-high-dose ICS, no ICS) • Smoking status at screening (current, former) • Number of moderate or severe COPD exacerbation in 1 year prior to visit 1 (≤2, 3, ≥4) • Number of severe COPD exacerbations in 1 year prior to visit 1 (0, 1, ≥2) • Baseline predicted post-bronchodilator FEV, % (<50%, ≥50%) • Baseline pre-bronchodilator FEV (<Median, ≥Median) • Baseline FEV, reversibility (<12%, ≥12%) • Baseline FEV, reversibility (<Median, ≥Median) • Baseline fractional exhaled nitiric oxide (20 20 ppb, ≥20 ppb) • Baseline plasma eotaxin-3 (<Median, ≥Median) • Baseline serum total IgE (<100 IU/ml, ≥100 IU/ml) • Baseline serum PARC (<Median, ≥Median) • Baseline fibrinogen (<350mg/dL, ≥350mg/dL) • Maximum eosinophil counts during screening (<500 cells/µL, ≥500 cells/µL)

Trial name: BOREAS	NCT number: NCT03930732
	In the BOREAS trial, the following endpoints were analysed in a pre-specified FENO ≥20 ppb subgroup: • Change in pre-BD FEV1 from baseline to week 12 in the subgroup of patients with baseline FENO ≥20 ppb • Change in pre-BD FEV1 from baseline to week 52 in the subgroup of patients with baseline FENO ≥20 ppb • Annualised rate of moderate or severe COPD exacerbation compared to placebo over the 52-week treatment period in the subgroup of patients with baseline FENO ≥20 ppb
Other relevant information	None.

Table 67 Main characteristic of NOTUS

Trial name: NOTUS	NCT number: NCT04456673
Objective	The purpose of the NOTUS trial was to investigate the efficacy, safety, and tolerability of dupilumab administered every 2 weeks among patients with moderate-to-severe type 2 inflammatory COPD over 52 weeks
Publications – title, author, journal, year	Abstract: Surya P. Bhatt, M.D., M.S.P.H., Klaus F. Rabe, M.D., Ph.D., Nicola A. Hanania, M.D., Claus F. Vogelmeier, M.D., Mona Bafadhel, M.D., Ph.D., Stephanie A. Christenson, M.D., Alberto Papi, M.D: Dupilumab for COPD with Blood Eosinophil Evidence of Type 2 Inflammation. N Engl J Med May 2020. DOI: 10.1056/NEJMoa2401304.
Study type and design	A randomised, double-blind, placebo-controlled, parallel-group, 52-week pivotal study
Sample size (n)	A total of 935 patients underwent randomisation: 470 were assigned to the dupilumab group and 465 to the placebo group (6).

Trial name: NOTUS	NCT number: NCT04456673



Main inclusion criteria

Inclusion criteria form clinicaltrials.gov:

- Participants with a physician diagnosis of COPD who meet the following criteria at screening:
    - Current or former smokers with a smoking history of ≥10 pack-years.
    - Moderate-to-severe COPD (post-bronchodilator FEV1/ forced vital capacity [FVC] ratio <0.70 and post-bronchodilator FEV1 % predicted >30% and ≤70%).
    - Medical Research Council (MRC) Dyspnea Scale grade ≥2.
    - 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 or ≥1 severe within the year prior to inclusion. At least one exacerbation should have occurred while the patient was taking ICS/LABA/LAMA (or LABA/LAMA if ICS is contraindicated). Moderate exacerbations are recorded by the investigator and defined as AECOPD that require either systemic corticosteroids (intramuscular, intravenous, or oral) and/or antibiotics. One

Trial name: NOTUS	NCT number: NCT04456673
	of the two required moderate exacerbations has to require the use of systemic corticosteroids. Severe exacerbations are recorded by the investigator and defined as AECOPD requiring hospitalization or observation > 24 hours in emergency department/urgent care facility. ○ Background triple therapy (ICS + LABA + LAMA) 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 is contraindicated. • Evidence of Type 2 inflammation: Patients with blood eosinophils ≥300 cells/microliter at Visit 1.
Main exclusion criteria	**Exclusion criteria from clinicaltrials.gov:** • COPD diagnosis for less than 12 months prior to randomisation. • Participants with current diagnosis of asthma according to the GINA guidelines, or documented history of asthma. • Significant pulmonary disease other than COPD (e.g., lung fibrosis, sarcoidosis, interstitial lung disease, pulmonary hypertension, bronchiectasis, Churg-Strauss Syndrome etc) or another diagnosed pulmonary or systemic disease associated with elevated peripheral eosinophil counts. • Cor pulmonale, evidence of right cardiac failure. • Long-term treatment with oxygen >4.0 L/min OR if a participant requires more than 2.0 L/min in order to maintain oxygen saturation >88%. • Hypercapnia requiring Bi-level ventilation. • AECOPD as defined in inclusion criteria within 4 weeks prior to screening, or during the screening period. • Respiratory tract infection within 4 weeks prior to screening, or during the screening period. • History of, or planned pneumonectomy or lung volume reduction surgery. Patients who are participating in the acute phase of a pulmonary rehabilitation program, i.e. who started rehabilitation <4 weeks prior to screening (Note: patients in the maintenance phase of a rehabilitation program can be included). Diagnosis of α-1 anti-trypsin deficiency.
Intervention	Dupilumab SC 300 mg every two weeks for 52 weeks
Comparator(s)	Placebo to match the intervention

Trial name: NOTUS	NCT number: NCT04456673
Follow-up time	4-week screening period, 52-week treatment period and 12-weeks follow-up period
Is the study used in the health economic model?	Yes

Primary, secondary and exploratory endpoints	Primary endpoint:
	• The primary endpoint was the annualized rate of moderate or severe COPD exacerbations over the 52-week treatment period
	Secondary endpoints:
	• Change in pre-BD FEV1 from baseline to week 12
	• Change in pre-BD FEV1 from baseline to week 52
	• Change from baseline to week 52 in the SGRQ total score
	• Proportion of patients with SGRQ score improvement from baseline ≥4 points at week 52
	• Change in pre-BD FEV1 from baseline through weeks other than 12 and 52 (i.e., weeks 2, 4, 8, 24, 36, and 44)
	• Change in post-BD FEV1 from baseline to weeks 2, 4, 8, 12, 24, 36 and 52
	• Change in forced expiratory flow (FEF) 25-75% from baseline to weeks 2, 4, 8, 12, 24, 36, 44, and 52
	• Annualized rate of severe COPD exacerbations compared to placebo over the 52-week treatment period
	• Time-to-first moderate or severe COPD exacerbation compared with placebo during the 52-week treatment period
	Exploratory endpoints:
	• Serum functional dupilumab concentrations and PK profile
	• Pharmacodynamic response of selected biomarkers
	  ○ Pulmonary and activation-regulated chemokine (PARC)
	  ○ Eotaxin-3
	  ○ Fractional exhaled nitric oxide (FeNO post-bronchodilator)
	  ○ Total IgE
	• Fibrinogen
	• Optional: Messenger ribonucleic acid (mRNA) sequencing or whole transcriptome analysis from blood

Trial name: NOTUS	NCT number: NCT04456673

- Optional: Deoxyribonucleic acid (DNA) for assessment of pharmacogenomic effects
- Annualized loss of lung function as assessed by a FEV1 slope analysis
- Change from baseline in FVC (% predicted and absolute values in mL) from baseline to Week 12, Week 24 and Week 52
- Evaluation of clinical respiratory symptoms of COPD using the Evaluating Respiratory Symptoms in COPD (E-RS: COPD) comprised in the EXACT tool
- Annualized rate of COPD exacerbations assessed by the EXACT over 52 week
- Increase in number of controller medication after exacerbation
- Increase in patient total daily dose of controller medication after exacerbation

Method of analysis	The primary analysis population for the efficacy endpoints was the ITT population, defined as all randomized participants analysed according to the treatment group allocated by randomisation. The week 52 efficacy endpoints (continuous and proportion type) were analysed using the ITT population with an opportunity to reach week 52 (i.e., completed the week 52 study period or would have completed had they not discontinued). The annualised rate of moderate or severe COPD exacerbation events (primary endpoint) was analysed using a negative binomial regression model. The analysis was also performed in the baseline FeNO ≥20 ppb subgroup. The model included the total number of events that occurred during the 52-week study intervention period as the response variable, with the following covariates: treatment group, region (pooled country), ICS dose at baseline (high-dose ICS [yes/no]), smoking status at screening (current smokers or not), baseline disease severity (as % predicted post-BD FEV_1), and number of moderate or severe COPD exacerbation events within 1 year prior to the study (≤2, 3, or ≥4). Log-transformed observation duration was used as offset variable. The estimated annualised event rate for each treatment group and its two-sided 95% CIs was derived. The event rate ratio of the dupilumab group against the placebo group, its two-sided 95% CI, and p-value were provided. The change from baseline in pre-BD FEV_1 and change from baseline in SGRQ total score were analysed using MMRM. The proportion of participants with SGRQ improvement ≥4 points was analysed using a logistic regression model.
Subgroup analyses	None
Other relevant information	None

Appendix B. Efficacy results per study

Results per study

In the following tables, we present results per study from BORAS and NOTUS.

Table 68 Results per study from the BOREAS trial, total population (ITT)

Results of BOREAS (NCT03930732)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Annualised rate of moderate or severe exacerbations of COPD	Dupilumab	468	0.78 (0.64, 0.93)	-0.33	-0.46, -0.15	Not reported	0.70	(0.58, 0.86)	<0.001	Relative risk presented. Absolute difference estimated based on the relative risk with the rate from the comparator arm.	Bhatt et al. 2023 (5)
	Placebo	471	1.10 (0.93, 1.30)								
Change in prebronchodilator FEV1 from baseline to week 52	Dupilumab	468	0.153 (0.116, 0.189)	N/A	N/A	N/A	0.083	(0.038, 0.128)	<0.001	Least-squares mean change in liters is presented and the difference in least-squares mean difference in liters.	Bhatt et al. 2023 (5)
	Placebo	471	0.070 (0.033, 0.107)								
	Placebo	471	43.1% (38.6, 47.7)								

Table 69 Results per study from the NOTUS trial, ITT

Results of NOTUS (NCT04456673)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Annualised rate of moderate or severe exacerbations of COPD	Dupilumab	470	0.859 (95% CI: 0.699, 1.057)	-0.435	-0.602, -0.229	Not reported	0.664	0.535, 0.823	0.0002	Relative risk presented. Absolute difference estimated based on the relative risk with the rate from the comparator arm.	Bhatt et al. 2024 (6)
	Placebo	465	1.295 (95% CI: 1.048, 1.600)								
Change in prebronchodilator FEV1 from baseline to week 52	Dupilumab	362	+0.115 (SE: 0.021) liter	N/A	N/A	N/A	+0.062 liter	95% CI: 0.011, 0.113	0.0182	Least-squares mean change in liters is presented and the difference in least-squares mean difference.	Bhatt et al. 2024 (6)
	Placebo	359	+0.054 (SE: 0.020) liter								

Table 70 Results per study from the pooled analysis of BOREAS and NOTUS trials, ITT

Results from pooled analysis of BOREAS and NOTUS											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Annualised rate of moderate or severe exacerbations of COPD	Dupilumab	938	0.794 (95% CI: 0.686, 0.920)	-0.362	-0.468, -0.239	Not reported	0.687	0.595, 0.793	<.0001	Relative risk presented. Absolute difference estimated based on the relative risk with the rate from the comparator arm.	Sanofi data on file
	Placebo	936	1.156 (95% CI: 1.005, 1.330)								
Change in prebronchodilator FEV1 from baseline to week 52	Dupilumab	830	0.133 (SE: 0.015)	N/A	N/A	N/A	0.073	0.040, 0.107	<.0001	Least-squares mean change in liters is presented and the difference in least-squares mean difference.	Sanofi data on file
	Placebo	830	0.059 (SE: 0.015)								

Appendix C. Comparative analysis of efficacy

As the BORAS and NOTUS trials are head-to-head trials, no comparative analyses are presented in this section. Please see Appendix B for the direct comparative analyses of dupilumab and placebo.

Table 71 Comparative analysis of studies comparing dupilumab to placebo for patients with moderate to severe COPD with type-2 inflammation, N/A

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
N/A									
N/A									
N/A									
N/A									

Appendix D. Extrapolation

D.1 Extrapolation of [effect measure 1]

N/A as no extrapolation was conducted in the present application.

D.1.1 Data input

N/A

D.1.2 Model

N/A

D.1.3 Proportional hazards

N/A

D.1.4 Evaluation of statistical fit (AIC and BIC)

N/A

D.1.5 Evaluation of visual fit

N/A

D.1.6 Evaluation of hazard functions

N/A

D.1.7 Validation and discussion of extrapolated curves

N/A

D.1.8 Adjustment of background mortality

N/A

D.1.9 Adjustment for treatment switching/cross-over

N/A

D.1.10 Waning effect

N/A

D.1.11 Cure-point

N/A

D.2 Extrapolation of [effect measure 2]

N/A

Appendix E. Serious adverse events

Table 72 presents the SAEs observed in the BOREAS trial. Only SAEs from the BOREAS are presented due to the similarities between BOREAS and the NOTUS and the low percentages of patients experiencing SAEs in the trials.

Table 72 SAEs by primary SOC and PT observed in the BOREAS trial (safety population). Source: CSR data on file.

SAE	Dupilumab (N=469)	Placebo (N=470)
Infections and infestations		
Pneumonia	XXX	XXX
COVID-19	XXX	XXX
Lower respiratory tract infection	XXX	XXX
COVID-19 pneumonia	XXX	XXX
Abdominal wall abscess	XXX	XXX
Bronchopulmonary aspergillosis	XXX	XXX
Cholecystitis infective	XXX	XXX
Epiglottitis	XXX	XXX
Herpes zoster	XXX	XXX
Pulmonary tuberculosis	XXX	XXX
Respiratory tract infection	XXX	XXX
Upper respiratory tract infection	XXX	XXX
Urinary tract infection	XXX	XXX
Appendicitis	XXX	XXX
Bronchitis bacterial	XXX	XXX
Influenza	XXX	XXX
Pneumonia bacterial	XXX	XXX
Pneumonia pneumococcal	XXX	XXX

SAE	Dupilumab (N=469)	Placebo (N=470)
Septic shock	XXX	XXX
Subcutaneous abscess	XXX	XXX
Neoplasm benign, malignant, and unspecified (incl. cyst and polyps)		
Bladder transitional cell carcinoma	XXX	XXX
Glioblastoma	XXX	XXX
Lung carcinoma cell type unspecified stage IV	XXX	XXX
Lung neoplasm	XXX	XXX
Lung neoplasm malignant	XXX	XXX
Rectal cancer	XXX	XXX
Squamous cell carcinoma of lung	XXX	XXX
Ductal adenocarcinoma of pancreas	XXX	XXX
Invasive ductal breast carcinoma	XXX	XXX
Lung adenocarcinoma	XXX	XXX
Pancreatic carcinoma metastatic	XXX	XXX
Prostate cancer	XXX	XXX
Squamous cell carcinoma of skin	XXX	XXX
Blood and lymphatic system disorders		
Anaemia	XXX	XXX
Polycythaemia	XXX	XXX
Blood loss anaemia	XXX	XXX
Immune system disorders		
Hypersensitivity	XXX	XXX
Anaphylactic reaction	XXX	XXX
Endocrine disorders		

SAE	Dupilumab (N=469)	Placebo (N=470)
Hyperparathyroidism	XXX	XXX
Metabolism and nutrition disorders		
Diabetes mellitus inadequate control	XXX	XXX
Hypokalaemia	XXX	XXX
Hyponatraemia	XXX	XXX
Type 2 diabetes mellitus	XXX	XXX
Psychiatric disorders		
Psychotic disorder	XXX	XXX
Nervours system disorders		
Cerebral haemorrhage	XXX	XXX
Generalised tonic-clonic seizure	XXX	XXX
Ischaemic stroke	XXX	XXX
Syncope	XXX	XXX
Basal ganglia haemorrhage	XXX	XXX
Cerebral infarction	XXX	XXX
Cerebrovascular accident	XXX	XXX
Presyncope	XXX	XXX
Transient ischaemic attack	XXX	XXX
Cardiac disorders		
Cardiac failure	XXX	XXX
Coronary artery disease	XXX	XXX
Acute coronary syndrome	XXX	XXX
Acute myocaridal infarction	XXX	XXX
Atrial fibrillation	XXX	XXX

SAE	Dupilumab (N=469)	Placebo (N=470)
Atrioventricular block second degree	XXX	XXX
Nodal rhythm	XXX	XXX
Angina unstable	XXX	XXX
Arrhythmia	XXX	XXX
Atrioventricular block complete	XXX	XXX
Cardiac failure congestive	XXX	XXX
Cor pulmonale acute	XXX	XXX
Myocardial infaction	XXX	XXX
Tachycardia	XXX	XXX
Vascular disorders		
Hypertensive crisis	XXX	XXX
Deep vein trombosis	XXX	XXX
Hypertensive emergency	XXX	XXX
Peripheral artery occlusion	XXX	XXX
Peripheral vascular disorder	XXX	XXX
Respiratory, thoracic and mediastinal disorders		
Chronic obstructive pulmonary disease	XXX	XXX
Acute pulmonary oedema	XXX	XXX
Acute respiratory failure	XXX	XXX
Atelectasis	XXX	XXX
Pneumothorax	XXX	XXX
Respiratory failure	XXX	XXX
Acute respiratory distress syndrome	XXX	XXX
Bronchospasm	XXX	XXX

SAE	Dupilumab (N=469)	Placebo (N=470)
Chronic respiratory failure	XXX	XXX
Pneumothorax spontaneous	XXX	XXX
Pulmonary oedema	XXX	XXX
Gastrointestinal disorders		
Colitis	XXX	XXX
Intestinal polyp	XXX	XXX
Pancreatitis acute	XXX	XXX
Umbilical hernia	XXX	XXX
Upper gastrointestinal haemorrhage	XXX	XXX
Abdominal pain	XXX	XXX
Gastritis	XXX	XXX
Intestinal ischaemia	XXX	XXX
Pancreatitis	XXX	XXX
Rectal haemorrhage	XXX	XXX
Hepatobiliary disorders		
Cholecystitis	XXX	XXX
Cholecystitis acute	XXX	XXX
Cholelithaiasis	XXX	XXX
Hepatic failure	XXX	XXX
Hepatorenal syndrome	XXX	XXX
Bile duct stone	XXX	XXX
Hepatic function abnormal	XXX	XXX
Musculoskeletal and connective tissue disorders		
Rhabdomyolysis	XXX	XXX

SAE	Dupilumab (N=469)	Placebo (N=470)
Renal and urinary disorders		
Chronic kidney disease	XXX	XXX
Haematuria	XXX	XXX
Renal failure	XXX	XXX
Acute kidney injury	XXX	XXX
Glomerulonephritis	XXX	XXX
Nephritis	XXX	XXX
Reproductive system and breast disorders		
Ovarian cyst	XXX	XXX
General disorders and administration site conditions		
Chest pain	XXX	XXX
Pyrexia	XXX	XXX
Sudden caridac death	XXX	XXX
Injury, poisoning and procedural complications		
Ankle fracture	XXX	XXX
Fibula fracture	XXX	XXX
Head injury	XXX	XXX
Pneumothorax traumatic	XXX	XXX
Road traffic accident	XXX	XXX
Skin abrasion	XXX	XXX
Tibia fracture	XXX	XXX
Femoral neck fracture	XXX	XXX
Femur fracture	XXX	XXX
Rib fracture	XXX	XXX

SAE	Dupilumab (N=469)	Placebo (N=470)
Spinal compression fracture	XXX	XXX

Table note: Table sorted by SOC internationally agreed order and decreasing percentage of PT in dupilumab group. The table presents the number and percentage of patients with at least one treatment-emergent SAE.
Abbreviations: SAE: serious adverse events, SOC: system organ class, PT: preferred term.

Table 73 Number (%) of patients with treatment-emergent SAE by primary SOC and PT in the safety population

SAE	Dupilumab (N=469)	Placebo (N=464)
Any class	XXX	XXX
INFECTIONS AND INFESTATIONS	XXX	XXX
Pneumonia	XXX	XXX
COVID-19 pneumonia	XXX	XXX
COVID-19	XXX	XXX
Pneumonia bacterial	XXX	XXX
Viral upper respiratory tract infection	XXX	XXX
Bacterial colitis	XXX	XXX
Clostridium difficile colitis	XXX	XXX
Diverticulitis	XXX	XXX
Gastrointestinal infection	XXX	XXX
Infective exacerbation of chronic obstructive airways disease	XXX	XXX
Influenza	XXX	XXX
Orchitis	XXX	XXX
Pneumonia pneumococcal	XXX	XXX
Pneumonia streptococcal	XXX	XXX
Respiratory tract infection	XXX	XXX
Suspected COVID-19	XXX	XXX

SAE	Dupilumab (N=469)	Placebo (N=464)
Anal abscess	xxx	xxx
Bronchitis	xxx	xxx
Lower respiratory tract infection bacterial	Xxx	Xxx
Nasal candidiasis	Xxx	Xxx
Oropharyngeal candidiasis	Xxx	xxx
Pneumonia klebsiella	xxx	Xxx
Pneumonia pseudomonal	Xxx	xxx
Urinary tract infection	xxx	Xxx
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	Xxx	xxx
Adenocarcinoma of colon	xxx	Xxx
Papillary thyroid cancer	Xxx	xxx
Prostate cancer	xxx	xxx
Squamous cell carcinoma of skin	Xxx	Xxx
Chronic myelomonocytic leukaemia	Xxx	Xxx
Invasive ductal breast carcinoma	Xxx	xxx
Squamous cell carcinoma of lung	Xxx	Xxx
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Xxx	Xxx
Autoimmune haemolytic anaemia	Xxx	Xxx
Iron deficiency anaemia	Xxx	Xxx
Anaemia	Xxx	xxx
IMMUNE SYSTEM DISORDERS	Xxx	Xxx
Anaphylactic reaction	Xxx	Xxx
ENDOCRINE DISORDERS	Xxx	Xxx
Inappropriate antidiuretic hormone secretion	Xxx	xxx

SAE	Dupilumab (N=469)	Placebo (N=464)
METABOLISM AND NUTRITION DISORDERS	xxx	xxx
Decreased appetite	xxx	xxx
Hyponatraemia	xxx	xxx
Hyperkalaemia	xxx	xxx
NERVOUS SYSTEM DISORDERS	xxx	xxx
Cerebral infarction	xxx	xxx
Cerebrovascular accident	xxx	xxx
Headache	xxx	xxx
Ischaemic stroke	xxx	xxx
Lacunar stroke	Xxx	xxx
Syncope	xxx	xxx
Transient ischaemic attack	xxx	xxx
Vocal cord paralysis	xxx	xxx
EYE DISORDERS	xxx	xxx
Cataract	xxx	Xxx
CARDIAC DISORDERS	xxx	xxx
Cardiac failure congestive	xxx	xxx
Atrial fibrillation	xxx	xxx
Cardiac arrest	xxx	Xxx
Cardiac failure	xxx	xxx
Cardiogenic shock	xxx	xxx
Cor pulmonale	xxx	xxx
Mitral valve incompetence	xxx	xxx
Sinus node dysfunction	xxx	xxx

SAE	Dupilumab (N=469)	Placebo (N=464)
Supraventricular tachycardia	xxx	xxx
Acute myocardial infarction	xxx	xxx
Angina pectoris	xxx	xxx
Angina unstable	xxx	xxx
Cardiovascular disorder	xxx	xxx
Myocardial infarction	xxx	xxx
Myocardial ischaemia	xxx	xxx
Postinfarction angina	xxx	xxx
Ventricular arrhythmia	xxx	xxx
VASCULAR DISORDERS	xxx	xxx
Deep vein thrombosis	xxx	xxx
Hypertensive crisis	Xxx	Xxx
Extremity necrosis	Xxx	xxx
Peripheral arterial occlusive disease	Xxx	xxx
Peripheral vascular disorder	Xxx	xxx
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Xxx	xxx
Chronic obstructive pulmonary disease	xxx	xxx
Pneumothorax	xxx	xxx
Hydrothorax	xxx	xxx
Hypoxia	xxx	xxx
Pleurisy	xxx	xxx
GASTROINTESTINAL DISORDERS	xxx	xxx
Abdominal hernia	xxx	Xxx
Abdominal pain	xxx	xxx

SAE	Dupilumab (N=469)	Placebo (N=464)
Upper gastrointestinal haemorrhage	xxx	xxx
Large intestinal stenosis	xxx	xxx
Small intestinal obstruction	xxx	xxx
Subileus	xxx	xxx
HEPATOBILIARY DISORDERS	xxx	xxx
Cholecystitis	xxx	xxx
RENAL AND URINARY DISORDERS	xxx	xxx
Acute kidney injury	xxx	xxx
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	xxx	xxx
Benign prostatic hyperplasia	xxx	xxx
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	xxx	xxx
Sudden death	xxx	xxx
Death	xxx	xxx
Non-cardiac chest pain	xxx	xxx
Sudden cardiac death	xxx	xxx
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	xxx	xxx
Ankle fractur	xxx	xxx
Thermal burn	xxx	xxx
Tibia fracture	xxx	xxx
Fall	xxx	xxx
Femur fracture	xxx	xxx

Appendix F. Health-related quality of life

Not applicable.

Appendix G. Probabilistic sensitivity analyses

Table 74 shows all parameters included in the PSA including the point estimate, and lower and upper bound and selected probability distributions used in the PSA.

Table 74 Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Probabilities				
Baseline%: Mild COPD	0.00	0.00	1000.00	Beta Dirichlet
Baseline%: Moderate COPD	0.50	500.00	500.00	Beta Dirichlet
Baseline%: Severe COPD	0.50	500.00	500.00	Beta Dirichlet
Baseline%: Very Severe COPD	0.00	0.00	1000.00	Beta Dirichlet
ExaRisk Baseline: Moderate exa - Mild COPD	0.16	100.00	0.00	Gamma
ExaRisk Baseline: Moderate exa - Moderate COPD	0.66	100.00	0.01	Gamma
ExaRisk Baseline: Moderate exa - Severe COPD	0.89	100.00	0.01	Gamma
ExaRisk Baseline: Moderate exa - Very Severe COPD	1.26	100.00	0.01	Gamma
ExaRisk Baseline: Severe exa - Mild COPD	0.00	0.00	0.00	Gamma
ExaRisk Baseline: Severe exa - Moderate COPD	0.06	100.00	0.00	Gamma
ExaRisk Baseline: Severe exa - Severe COPD	0.11	100.00	0.00	Gamma
ExaRisk Baseline: Severe exa - Very Severe COPD	0.07	100.00	0.00	Gamma
ExaRisk RespTrial: Moderate exa - Mild COPD	0.19	100.00	0.00	Gamma

ExaRisk RespTrial: Moderate exa - Moderate COPD	0.29	100.00	0.00	Gamma
ExaRisk RespTrial: Moderate exa - Severe COPD	0.36	100.00	0.00	Gamma
ExaRisk RespTrial: Moderate exa - Very Severe COPD	0.49	100.00	0.00	Gamma
ExaRisk RespTrial: Severe exa - Mild COPD	0.00	0.00	0.00	Gamma
ExaRisk RespTrial: Severe exa - Moderate COPD	0.01	0.12	0.08	Gamma
ExaRisk RespTrial: Severe exa - Severe COPD	0.03	0.69	0.04	Gamma
ExaRisk RespTrial: Severe exa - Very Severe COPD	0.04	0.67	0.06	Gamma
ExaRisk AllTrial: Moderate exa - Mild COPD	0.24	100.00	0.00	Gamma
ExaRisk AllTrial: Moderate exa - Moderate COPD	0.44	100.00	0.00	Gamma
ExaRisk AllTrial: Moderate exa - Severe COPD	0.77	100.00	0.01	Gamma
ExaRisk AllTrial: Moderate exa - Very Severe COPD	0.81	100.00	0.01	Gamma
ExaRisk AllTrial: Severe exa - Mild COPD	0.02	0.69	0.03	Gamma
ExaRisk AllTrial: Severe exa - Moderate COPD	0.04	0.83	0.05	Gamma
ExaRisk AllTrial: Severe exa - Severe COPD	0.07	0.83	0.08	Gamma
ExaRisk AllTrial: Severe exa - Very Severe COPD	0.07	0.75	0.09	Gamma
Reference moderate exacerbation Rate - Whittaker 2022 - Mild COPD	0.50	100.00	0.01	Gamma
Reference moderate exacerbation Rate - Whittaker 2022 - Moderate COPD	0.61	100.00	0.01	Gamma

Reference moderate exacerbation Rate - Whittaker 2022 - Severe COPD	1.02	100.00	0.01	Gamma
Reference moderate exacerbation Rate - Whittaker 2022 - Very severe COPD	0.82	100.00	0.01	Gamma
Reference severe exacerbation Rate - Whittaker 2022 - Mild COPD	0.10	100.00	0.00	Gamma
Reference severe exacerbation Rate - Whittaker 2022 - Moderate COPD	0.11	100.00	0.00	Gamma
Reference severe exacerbation Rate - Whittaker 2022 - Severe COPD	0.20	100.00	0.00	Gamma
Reference severe exacerbation Rate - Whittaker 2022 - Very severe COPD	0.34	100.00	0.00	Gamma
% end of amelioration Dupi: Mild COPD	0.06	58.29	941.71	Gamma Dirichlet
% end of amelioration Dupi: Moderate COPD	0.52	519.87	480.13	Gamma Dirichlet
% end of amelioration Dupi: Severe COPD	0.39	392.98	607.02	Gamma Dirichlet
% end of amelioration Dupi: Very Severe COPD	0.03	28.86	971.14	Gamma Dirichlet
% end of amelioration SOC: Mild COPD	0.03	32.91	967.09	Gamma Dirichlet
% end of amelioration SOC: Moderate COPD	0.52	519.41	480.59	Gamma Dirichlet
% end of amelioration SOC: Severe COPD	0.42	421.77	578.23	Gamma Dirichlet
% end of amelioration SOC: Very Severe COPD	0.03	25.91	974.09	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Mild COPD, No exacerbation	0.89	891.93	108.07	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Mild COPD, Moderate exacerbation	0.77	766.83	233.17	Gamma Dirichlet

No Exa, Exa Event Per Cycle (const), Dupi: Mild COPD, Severe exacerbation	0.75	745.72	254.28	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Moderate COPD, No exacerbation	0.81	806.43	193.57	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Moderate COPD, Moderate exacerbation	0.60	604.83	395.17	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Moderate COPD, Severe exacerbation	0.57	565.20	434.80	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Severe COPD, No exacerbation	0.68	679.91	320.09	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Severe COPD, Moderate exacerbation	0.40	395.41	604.59	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Severe COPD, Severe exacerbation	0.33	330.98	669.02	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Very Severe COPD, No exacerbation	0.67	668.05	331.95	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Very Severe COPD, Moderate exacerbation	0.38	377.25	622.75	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Very Severe COPD, Severe exacerbation	0.31	312.77	687.23	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Mild COPD, No exacerbation	0.89	891.93	108.07	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Mild COPD, Moderate exacerbation	0.77	766.83	233.17	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Mild COPD, Severe exacerbation	0.75	745.72	254.28	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Moderate COPD, No exacerbation	0.81	806.43	193.57	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Moderate COPD, Moderate exacerbation	0.60	604.83	395.17	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Moderate COPD, Severe exacerbation	0.57	565.20	434.80	Gamma Dirichlet

No Exa, Exa Event Per Cycle (const), Dupi: Severe COPD, No exacerbation	0.68	679.91	320.09	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Severe COPD, Moderate exacerbation	0.40	395.41	604.59	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Severe COPD, Severe exacerbation	0.33	330.98	669.02	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Very Severe COPD, No exacerbation	0.67	668.05	331.95	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Very Severe COPD, Moderate exacerbation	0.38	377.25	622.75	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Very Severe COPD, Severe exacerbation	0.31	312.77	687.23	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Mild COPD, No exacerbation	0.89	891.93	108.07	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Mild COPD, Moderate exacerbation	0.77	766.83	233.17	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Mild COPD, Severe exacerbation	0.75	745.72	254.28	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Moderate COPD, No exacerbation	0.81	806.43	193.57	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Moderate COPD, Moderate exacerbation	0.60	604.83	395.17	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Moderate COPD, Severe exacerbation	0.57	565.20	434.80	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Severe COPD, No exacerbation	0.68	679.91	320.09	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Severe COPD, Moderate exacerbation	0.40	395.41	604.59	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Severe COPD, Severe exacerbation	0.33	330.98	669.02	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Very Severe COPD, No exacerbation	0.67	668.05	331.95	Gamma Dirichlet

No Exa, Exa Event Per Cycle (const), Dupi: Very Severe COPD, Moderate exacerbation	0.38	377.25	622.75	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), Dupi: Very Severe COPD, Severe exacerbation	0.31	312.77	687.23	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), SOC: Mild COPD, No exacerbation	0.94	936.53	63.47	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), SOC: Mild COPD, Moderate exacerbation	0.85	852.14	147.86	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), SOC: Mild COPD, Severe exacerbation	0.85	849.91	150.09	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), SOC: Moderate COPD, No exacerbation	0.72	720.46	279.54	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), SOC: Moderate COPD, Moderate exacerbation	0.46	458.62	541.38	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), SOC: Moderate COPD, Severe exacerbation	0.40	402.07	597.93	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), SOC: Severe COPD, No exacerbation	0.62	617.75	382.25	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), SOC: Severe COPD, Moderate exacerbation	0.31	306.49	693.51	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), SOC: Severe COPD, Severe exacerbation	0.21	213.65	786.35	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), SOC: Very Severe COPD, No exacerbation	0.55	547.21	452.79	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), SOC: Very Severe COPD, Moderate exacerbation	0.22	216.05	783.95	Gamma Dirichlet
No Exa, Exa Event Per Cycle (const), SOC: Very Severe COPD, Severe exacerbation	0.15	151.63	848.37	Gamma Dirichlet
>=1 Mod, Exa Event Per Cycle (const), SOC: Mild COPD, No exacerbation	0.06	63.47	936.53	Gamma Dirichlet
>=1 Mod, Exa Event Per Cycle (const), SOC: Mild COPD, Moderate exacerbation	0.15	147.86	852.14	Gamma Dirichlet

>=1 Mod, Exa Event Per Cycle (const), SOC: Mild COPD, Severe exacerbation	0.15	150.09	849.91	Gamma Dirichlet
>=1 Mod, Exa Event Per Cycle (const), SOC: Moderate COPD, No exacerbation	0.24	237.00	763.00	Gamma Dirichlet
>=1 Mod, Exa Event Per Cycle (const), SOC: Moderate COPD, Moderate exacerbation	0.48	483.15	516.85	Gamma Dirichlet
>=1 Mod, Exa Event Per Cycle (const), SOC: Moderate COPD, Severe exacerbation	0.49	488.71	511.29	Gamma Dirichlet
>=1 Mod, Exa Event Per Cycle (const), SOC: Severe COPD, No exacerbation	0.31	305.63	694.37	Gamma Dirichlet
>=1 Mod, Exa Event Per Cycle (const), SOC: Severe COPD, Moderate exacerbation	0.59	589.34	410.66	Gamma Dirichlet
>=1 Mod, Exa Event Per Cycle (const), SOC: Severe COPD, Severe exacerbation	0.60	595.29	404.71	Gamma Dirichlet
>=1 Mod, Exa Event Per Cycle (const), SOC: Very Severe COPD, No exacerbation	0.40	403.33	596.67	Gamma Dirichlet
>=1 Mod, Exa Event Per Cycle (const), SOC: Very Severe COPD, Moderate exacerbation	0.72	716.35	283.65	Gamma Dirichlet
>=1 Mod, Exa Event Per Cycle (const), SOC: Very Severe COPD, Severe exacerbation	0.72	722.14	277.86	Gamma Dirichlet
>=1 Severe, Exa Event Per Cycle (const), SOC: Mild COPD, No exacerbation	0.00	0.00	1000.00	Gamma Dirichlet
>=1 Severe, Exa Event Per Cycle (const), SOC: Mild COPD, Moderate exacerbation	0.00	0.00	1000.00	Gamma Dirichlet
>=1 Severe, Exa Event Per Cycle (const), SOC: Mild COPD, Severe exacerbation	0.00	0.00	1000.00	Gamma Dirichlet
>=1 Severe, Exa Event Per Cycle (const), SOC: Moderate COPD, No exacerbation	0.04	42.55	957.45	Gamma Dirichlet
>=1 Severe, Exa Event Per Cycle (const), SOC: Moderate COPD, Moderate exacerbation	0.06	58.24	941.76	Gamma Dirichlet
>=1 Severe, Exa Event Per Cycle (const), SOC: Moderate COPD, Severe exacerbation	0.11	109.21	890.79	Gamma Dirichlet

>=1 Severe, Exa Event Per Cycle (const), SOC: Severe COPD, No exacerbation	0.08	76.62	923.38	Gamma Dirichlet
>=1 Severe, Exa Event Per Cycle (const), SOC: Severe COPD, Moderate exacerbation	0.10	104.17	895.83	Gamma Dirichlet
>=1 Severe, Exa Event Per Cycle (const), SOC: Severe COPD, Severe exacerbation	0.19	191.06	808.94	Gamma Dirichlet
>=1 Severe, Exa Event Per Cycle (const), SOC: Very Severe COPD, No exacerbation	0.05	49.46	950.54	Gamma Dirichlet
>=1 Severe, Exa Event Per Cycle (const), SOC: Very Severe COPD, Moderate exacerbation	0.07	67.61	932.39	Gamma Dirichlet
>=1 Severe, Exa Event Per Cycle (const), SOC: Very Severe COPD, Severe exacerbation	0.13	126.22	873.78	Gamma Dirichlet
FEV change, Dupilumab To Mod, No ex	0.00	0.00	0.00	Beta
FEV change, Dupilumab To Mod, Mod ex	0.00	0.00	0.00	Beta
FEV change, Dupilumab To Mod, Sev ex	0.00	0.00	0.00	Beta
FEV change, Dupilumab To Sev, No ex	0.00	0.00	0.00	Beta
FEV change, Dupilumab To Sev, Mod ex	0.00	0.00	0.00	Beta
FEV change, Dupilumab To Sev, Sev ex	0.00	0.00	0.00	Beta
FEV change, Dupilumab To Very Sev, No ex	0.00	0.00	0.00	Beta
FEV change, Dupilumab To Very Sev, Mod ex	0.00	0.00	0.00	Beta
FEV change, Dupilumab To Very Sev, Sev ex	0.00	0.00	0.00	Beta
FEV change, SOC, To Mod, No ex	0.00	0.00	0.00	Beta
FEV change, SOC, To Mod, Mod ex	0.00	0.00	0.00	Beta
FEV change, SOC, To Mod, Sev ex	0.00	0.00	0.00	Beta
FEV change, SOC, To Sev, No ex	0.00	0.00	0.00	Beta

FEV change, SOC, To Sev, Mod ex	0.00	0.00	0.00	Beta
FEV change, SOC, To Sev, Sev ex	0.00	0.00	0.00	Beta
FEV change, SOC, To Very Sev, No ex	0.00	0.00	0.00	Beta
FEV change, SOC, To Very Sev, Mod ex	0.00	0.00	0.00	Beta
FEV change, SOC, To Very Sev, Sev ex	0.00	0.00	0.00	Beta
Whittaker 2022 IRR, No exacerbation history: moderate exacerbation	1.00	0.00	0.00	Lognormal
Whittaker 2022 IRR, 1 moderate exacerbation history: moderate exacerbation	1.78	0.57	0.18	Lognormal
Whittaker 2022 IRR, 2 moderate exacerbation history: moderate exacerbation	2.44	0.89	0.24	Lognormal
Whittaker 2022 IRR, 3+ moderate exacerbation history: moderate exacerbation	3.94	1.37	0.39	Lognormal
Whittaker 2022 IRR, 1 severe exacerbation history: moderate exacerbation	2.48	0.90	0.25	Lognormal
Whittaker 2022 IRR, 2 severe exacerbation history: moderate exacerbation	2.27	0.81	0.23	Lognormal
Whittaker 2022 IRR, 3+ severe exacerbation history: moderate exacerbation	2.15	0.76	0.22	Lognormal
Whittaker 2022 IRR, No exacerbation history: severe exacerbation	1.00	0.00	0.00	Lognormal
Whittaker 2022 IRR, 1 moderate exacerbation history: severe exacerbation	1.21	0.19	0.12	Lognormal
Whittaker 2022 IRR, 2 moderate exacerbation history: severe exacerbation	1.38	0.32	0.14	Lognormal
Whittaker 2022 IRR, 3+ moderate exacerbation history: severe exacerbation	1.70	0.53	0.17	Lognormal
Whittaker 2022 IRR, 1 severe exacerbation history: severe exacerbation	2.66	0.97	0.27	Lognormal

Whittaker 2022 IRR, 2 severe exacerbation history: severe exacerbation	3.86	1.35	0.39	Lognormal
Whittaker 2022 IRR, 3+ severe exacerbation history: severe exacerbation	5.35	1.67	0.54	Lognormal
SMR Mild COPD	1.00	0.00	0.05	Lognormal
SMR Moderate COPD	1.40	0.34	0.05	Lognormal
SMR Severe COPD	2.55	0.94	0.05	Lognormal
SMR Very Severe COPD	2.65	0.97	0.05	Lognormal
SMR Mortality adjustment factor	2.0	1.34	2.95	Lognormal
Mortality adjustment factor	4.95	1.60	0.50	Lognormal
Excess mort due to 1 mod exacerbation, Whittaker	1.08	0.07	0.11	Lognormal
Excess mort due to 2 mod exacerbation, Whittaker	1.16	0.14	0.12	Lognormal
Excess mort due to 3+ mod exacerbation, Whittaker	1.32	0.27	0.13	Lognormal
Excess mort due to 1 sev exacerbation, Whittaker	1.75	0.55	0.18	Lognormal
Excess mort due to 2 sev exacerbation, Whittaker	2.33	0.84	0.23	Lognormal
Excess mort due to 3+ sev exacerbation, Whittaker	2.87	1.05	0.29	Lognormal
Adjusted excess mort due to 1 mod exacerbation	5.35	1.67	0.54	Lognormal
Adjusted excess mort due to 2 mod exacerbation	5.75	1.74	0.57	Lognormal
Adjusted excess mort due to 3+ mod exacerbation	6.54	1.87	0.65	Lognormal
Adjusted excess mort due to 1 sev exacerbation	8.67	2.15	0.87	Lognormal

Adjusted excess mort due to 2 sev exacerbation	11.54	2.44	1.15	Lognormal
Adjusted excess mort due to 3+ sev exacerbation	14.22	2.65	1.42	Lognormal
Dupilumab + Background Therapy: AE Frequency: Nasopharyngitis	0.09	90.51	872.32	Beta
Dupilumab + Background Therapy: AE Frequency: Back Pain	0.05	94.85	1764.94	Beta
Dupilumab + Background Therapy: AE Frequency: COPD (exacerbation)	0.06	94.14	1529.00	Beta
Dupilumab + Background Therapy: AE Frequency: Diarrhea	0.05	94.65	1691.15	Beta
Dupilumab + Background Therapy: AE Frequency: COVID-19	0.04	95.86	2242.17	Beta
Background Therapy: AE Frequency: Nasopharyngitis	0.10	90.30	850.36	Beta
Background Therapy: AE Frequency: Back Pain	0.03	96.57	2743.61	Beta
Background Therapy: AE Frequency: COPD (exacerbation)	0.06	93.94	1471.73	Beta
Background Therapy: AE Frequency: Diarrhea				
Background Therapy: AE Frequency: COVID-19	0.06	94.24	1559.14	Beta
List price: Trelegy Ellipta (fluticasone/umeclidinium/vilanterol)	1080.50	100.00	10.81	Gamma
Unit cost: Outpatient visit, respiratory physician	1989.00	100.00	19.89	Gamma
Unit cost: Outpatient visit, GP	160.72	100.00	1.61	Gamma
Unit cost: Spirometry	429.00	100.00	4.29	Gamma
Unit cost: Influenza vaccination	160.17	100.00	1.60	Gamma

Unit cost: Oxygen therapy (days)	68.45	100.00	0.68	Gamma
Unit cost: ICU days	25983.51	100.00	259.84	Gamma
Unit cost: Inpatient, non-ICU days	2837.36	100.00	28.37	Gamma
Unit cost: ER visits	1989.00	100.00	19.89	Gamma
Unit cost: Visit other health care provider	160.72	100.00	1.61	Gamma
Unit cost: Pneumococcal vaccination	160.17	100.00	1.60	Gamma
Unit cost: Readmissions	31211.00	100.00	312.11	Gamma
Unit cost: Emergency ambulance transfer	1729.45	100.00	17.29	Gamma
Unit cost: Emergency nurse	462.00	100.00	4.62	Gamma
Transportation cost: Outpatient visit, respiratory physician	149.00	100.00	1.49	Gamma
Transportation cost: Outpatient visit, GP	149.00	100.00	1.49	Gamma
Transportation cost: Spirometry	149.00	100.00	1.49	Gamma
Transportation cost: Influenza vaccination	149.00	100.00	1.49	Gamma
Transportation cost: Oxygen therapy (days)	149.00	100.00	1.49	Gamma
Transportation cost: ICU days	149.00	100.00	1.49	Gamma
Transportation cost: Inpatient, non-ICU days	149.00	100.00	1.49	Gamma
Transportation cost: ER visits	149.00	100.00	1.49	Gamma
Transportation cost: Visit other health care provider	149.00	100.00	1.49	Gamma
Transportation cost: Pneumococcal vaccination	149.00	100.00	1.49	Gamma
Transportation cost: Readmissions	149.00	100.00	1.49	Gamma
Transportation cost: Emergency ambulance transfer	149.00	100.00	1.49	Gamma

Transportation cost: Emergency nurse	149.00	100.00	1.49	Gamma
Patient time use: Outpatient visit, respiratory physician	1.50	100.00	0.02	Gamma
Patient time use: Outpatient visit, GP	1.50	100.00	0.02	Gamma
Patient time use: Spirometry				
Patient time use: Influenza vaccination	1.50	100.00	0.02	Gamma
Patient time use: Oxygen therapy (days)	1.50	100.00	0.02	Gamma
Patient time use: ICU days	24.00	100.00	0.24	Gamma
Patient time use: Inpatient, non-ICU days	24.00	100.00	0.24	Gamma
Patient time use: ER visits	6.00	100.00	0.06	Gamma
Patient time use: Visit other health care provider	1.50	100.00	0.02	Gamma
Patient time use: Pneumococcal vaccination	1.50	100.00	0.02	Gamma
Patient time use: Readmissions	24.00	100.00	0.24	Gamma
Patient time use: Emergency ambulance transfer	1.00	100.00	0.01	Gamma
Patient time use: Emergency nurse	1.00	100.00	0.01	Gamma
Unit cost of patient hour	203.00	100.00	2.03	Gamma
Frequency per moderate exacerbation in Mod Exa Outpatient visit, respiratory physician	0.34	100.00	0.00	Gamma
Frequency per moderate exacerbation in Mod Exa Outpatient visit, GP	0.66	100.00	0.01	Gamma
Frequency per moderate exacerbation in Mod Exa Spirometry	0.00	0.00	0.00	Gamma
Frequency per moderate exacerbation in Mod Exa Influenza vaccination	0.00	0.00	0.00	Gamma

Frequency per moderate exacerbation in Mod Exa Oxygen therapy (days)	0.00	0.00	0.00	Gamma
Frequency per moderate exacerbation in Mod Exa ICU days	0.00	0.00	0.00	Gamma
Frequency per moderate exacerbation in Mod Exa Inpatient, non-ICU days	0.00	0.00	0.00	Gamma
Frequency per moderate exacerbation in Mod Exa ER visits	0.00	0.00	0.00	Gamma
Frequency per moderate exacerbation in Mod Exa Visit other health care provider	0.27	100.00	0.00	Gamma
Frequency per moderate exacerbation in Mod Exa Pneumococcal vaccination	0.00	0.00	0.00	Gamma
Frequency per moderate exacerbation in Mod Exa Readmissions	0.00	0.00	0.00	Gamma
Frequency per moderate exacerbation in Mod Exa Emergency ambulance transfer	0.30	100.00	0.00	Gamma
Frequency per moderate exacerbation in Mod Exa Emergency nurse	0.60	100.00	0.01	Gamma
Frequency of resources (annually) in moderate COPD in Sev Outpatient visit, respiratory physician	0.82	100.00	0.01	Gamma
Frequency of resources (annually) in moderate COPD in Sev Outpatient visit, GP	0.70	100.00	0.01	Gamma
Frequency of resources (annually) in moderate COPD in Sev Spirometry	0.00	0.00	0.00	Gamma
Frequency of resources (annually) in moderate COPD in Sev Influenza vaccination	0.00	0.00	0.00	Gamma
Frequency of resources (annually) in moderate COPD in Sev Oxygen therapy (days)	0.21	100.00	0.00	Gamma
Frequency of resources (annually) in moderate COPD in Sev ICU days	0.86	100.00	0.01	Gamma

Frequency of resources (annually) in moderate COPD in Sev Inpatient, non-ICU days	11.08	100.00	0.11	Gamma
Frequency of resources (annually) in moderate COPD in Sev ER visits	0.25	100.00	0.00	Gamma
Frequency of resources (annually) in moderate COPD in Sev Visit other health care provider	0.50	100.00	0.01	Gamma
Frequency of resources (annually) in moderate COPD in Sev Pneumococcal vaccination	0.00	0.00	0.00	Gamma
Frequency of resources (annually) in moderate COPD in Sev Readmissions	0.16	100.00	0.00	Gamma
Frequency of resources (annually) in moderate COPD in Sev Emergency ambulance transfer	0.90	100.00	0.01	Gamma
Frequency of resources (annually) in moderate COPD in Sev Emergency nurse	1.20	100.00	0.01	Gamma
Frequency of resources (annually) in mild COPD Outpatient visit, respiratory physician	0.00	0.00	0.00	Gamma
Frequency of resources (annually) in mild COPD Outpatient visit, GP	1.00	100.00	0.01	Gamma
Frequency of resources (annually) in mild COPD Spirometry	1.00	100.00	0.01	Gamma
Frequency of resources (annually) in mild COPD Influenza vaccination	0.75	100.00	0.01	Gamma
Frequency of resources (annually) in mild COPD Oxygen therapy (days)	0.00	0.00	0.00	Gamma
Frequency of resources (annually) in mild COPD ICU days	0.00	0.00	0.00	Gamma
Frequency of resources (annually) in mild COPD Inpatient, non-ICU days	0.25	100.00	0.00	Gamma
Frequency of resources (annually) in mild COPD ER visits	0.00	0.00	0.00	Gamma

Frequency of resources (annually) in mild COPD Visit other health care provider	1.00	100.00	0.01	Gamma
Frequency of resources (annually) in mild COPD Pneumococcal vaccination	0.00	0.00	0.00	Gamma
Frequency of resources (annually) in mild COPD Readmissions	0.03	100.00	0.00	Gamma
Frequency of resources (annually) in mild COPD Emergency ambulance transfer	0.00	0.00	0.00	Gamma
Frequency of resources (annually) in moderate COPD Outpatient visit, respiratory physician	1.00	100.00	0.01	Gamma
Frequency of resources (annually) in moderate COPD Outpatient visit, GP	2.00	100.00	0.02	Gamma
Frequency of resources (annually) in moderate COPD Spirometry	2.00	100.00	0.02	Gamma
Frequency of resources (annually) in moderate COPD Influenza vaccination	0.75	100.00	0.01	Gamma
Frequency of resources (annually) in moderate COPD Oxygen therapy (days)	0.00	0.00	0.00	Gamma
Frequency of resources (annually) in moderate COPD ICU days	0.00	0.00	0.00	Gamma
Frequency of resources (annually) in moderate COPD Inpatient, non-ICU days	1.00	100.00	0.01	Gamma
Frequency of resources (annually) in moderate COPD ER visits	0.00	0.00	0.00	Gamma
Frequency of resources (annually) in moderate COPD Visit other health care provider	2.00	100.00	0.02	Gamma
Frequency of resources (annually) in moderate COPD Pneumococcal vaccination	0.15	100.00	0.00	Gamma
Frequency of resources (annually) in moderate COPD Readmissions	0.05	100.00	0.00	Gamma

Frequency of resources (annually) in moderate COPD Emergency ambulance transfer	0.00	0.00	0.00	Gamma
Frequency of resources (annually) in moderate COPD Emergency nurse	0.00	0.00	0.00	Gamma
Frequency of resources (annually) in Severe COPD Outpatient visit, respiratory physician	2.00	100.00	0.02	Gamma
Frequency of resources (annually) in Severe COPD Outpatient visit, GP	2.00	100.00	0.02	Gamma
Frequency of resources (annually) in Severe COPD Spirometry	3.00	100.00	0.03	Gamma
Frequency of resources (annually) in Severe COPD Influenza vaccination	0.75	100.00	0.01	Gamma
Frequency of resources (annually) in Severe COPD Oxygen therapy (days)	35.00	100.00	0.35	Gamma
Frequency of resources (annually) in Severe COPD ICU days	2.00	100.00	0.02	Gamma
Frequency of resources (annually) in Severe COPD Inpatient, non-ICU days	2.00	100.00	0.02	Gamma
Frequency of resources (annually) in Severe COPD ER visits	0.00	0.00	0.00	Gamma
Frequency of resources (annually) in Severe COPD Visit other health care provider	3.00	100.00	0.03	Gamma
Frequency of resources (annually) in Severe COPD Pneumococcal vaccination	0.30	100.00	0.00	Gamma
Frequency of resources (annually) in Severe COPD Readmissions	0.20	100.00	0.00	Gamma
Frequency of resources (annually) in Severe COPD Emergency ambulance transfer	0.00	0.00	0.00	Gamma
Frequency of resources (annually) in Severe COPD Emergency nurse	0.00	0.00	0.00	Gamma

Frequency of resources (annually) in Very severe COPD Outpatient visit, respiratory physician	3.00	100.00	0.03	Gamma
Frequency of resources (annually) in Very severe COPD Outpatient visit, GP	2.00	100.00	0.02	Gamma
Frequency of resources (annually) in Very severe COPD Spirometry	3.00	100.00	0.03	Gamma
Frequency of resources (annually) in Very severe COPD Influenza vaccination	0.75	100.00	0.01	Gamma
Frequency of resources (annually) in Very severe COPD Oxygen therapy (days)	35.00	100.00	0.35	Gamma
Frequency of resources (annually) in Very severe COPD ICU days	2.00	100.00	0.02	Gamma
Frequency of resources (annually) in Very severe COPD Inpatient, non-ICU days	2.00	100.00	0.02	Gamma
Frequency of resources (annually) in Very severe COPD ER visits	0.00	0.00	0.00	Gamma
Frequency of resources (annually) in Very severe COPD Visit other health care provider	3.00	100.00	0.03	Gamma
Frequency of resources (annually) in Very severe COPD Pneumococcal vaccination	0.30	100.00	0.00	Gamma
Frequency of resources (annually) in Very severe COPD Readmissions	0.20	100.00	0.00	Gamma
Frequency of resources (annually) in Very severe COPD Emergency ambulance transfer	0.00	0.00	0.00	Gamma
Frequency of resources (annually) in Very severe COPD Emergency nurse	0.00	0.00	0.00	Gamma
Distribution of SOC: ICS/LAMA/LABA	1.00	100.00	0.00	Gamma Dirichlet
Distribution of SOC: LAMA/LABA	0.00	0.00	100.00	Gamma Dirichlet

Utility: Mild COPD	0.87	12.43	1.91	Beta
Utility: Moderate COPD	0.84	14.86	2.77	Beta
Utility: Severe COPD	0.79	20.11	5.31	Beta
Utility: Very severe COPD	0.77	22.74	6.98	Beta
Disutility: Moderate exacerbation - Acute	0.05	94.65	1691.15	Beta
Disutility: Severe exacerbation - Acute	0.09	91.21	957.21	Beta
Disutility: Moderate exacerbation - Chronic	0.01	98.69	7492.62	Beta
Disutility: Severe exacerbation - Chronic	0.02	97.88	4563.03	Beta
Disutility: Moderate exacerbation - Acute duration	1.00	0.00	0.00	Normal
Disutility: Severe exacerbation - Acute duration	1.00	0.00	0.00	Normal
Disutility: Moderate exacerbation - Chronic duration	12.00	0.00	0.00	Normal
Disutility: Severe exacerbation - Chronic duration	12.00	0.00	0.00	Normal
AE Disutility: Nasopharyngitis	0.00	0.00	0.00	Beta
AE Disutility: Back Pain	0.00	0.00	0.00	Beta
AE Disutility: COPD (exacerbation)	0.00	0.00	0.00	Beta
AE Disutility: Diarrhea	0.00	0.00	0.00	Beta
AE Disutility: COVID-19	0.00	0.00	0.00	Beta
AE Disutility Duration: Nasopharyngitis	0.59	0.00	0.00	Normal
AE Disutility Duration: Back Pain	0.34	0.00	0.00	Normal
AE Disutility Duration: COPD (exacerbation)	0.34	0.00	0.00	Normal
AE Disutility Duration: Diarrhea	0.16	0.00	0.00	Normal

AE Disutility Duration: COVID-19	0.00	0.00	0.00	Normal
COPD stage Mild	233.52	100.00	2.34	Gamma
COPD stage Moderate	233.52	100.00	2.34	Gamma
COPD stage Severe	777.08	100.00	7.77	Gamma
COPD stage Very severe	2400.61	100.00	24.01	Gamma
Exacerbation cost: Moderate	4645.26	100.00	46.45	Gamma
Exacerbation cost: Severe	52549.64	100.00	525.50	Gamma
AE costs: Nasopharyngitis	160.72	100.00	1.61	Gamma
AE costs: Back Pain	160.72	100.00	1.61	Gamma
AE costs: COPD (exacerbation)	2837.36	100.00	28.37	Gamma
AE costs: Diarrhea	160.72	100.00	1.61	Gamma
AE costs: COVID-19	160.72	100.00	1.61	Gamma
AE transportation costs: Nasopharyngitis	149.00	100.00	1.49	Gamma
AE transportation costs: Back Pain	149.00	100.00	1.49	Gamma
AE transportation costs: COPD (exacerbation)	149.00	100.00	1.49	Gamma
AE transportation costs: Diarrhea	149.00	100.00	1.49	Gamma
AE transportation costs: COVID-19	149.00	100.00	1.49	Gamma
AE transportation costs: Placeholder1	0.00	0.00	0.00	Gamma
AE transportation costs: Placeholder2	0.00	0.00	0.00	Gamma
AE transportation costs: Placeholder3	0.00	0.00	0.00	Gamma
AE transportation costs: Placeholder4	0.00	0.00	0.00	Gamma
AE transportation costs: Placeholder5	0.00	0.00	0.00	Gamma
AE transportation costs: Placeholder6	0.00	0.00	0.00	Gamma

AE transportation costs: Placeholder7	0.00	0.00	0.00	Gamma
AE visits: Nasopharyngitis	1.00	100.00	0.01	Gamma
AE visits: Back Pain	1.00	100.00	0.01	Gamma
AE visits: COPD (exacerbation)	1.00	100.00	0.01	Gamma
AE visits: Diarrhea	1.00	100.00	0.01	Gamma
AE visits: COVID-19	1.00	100.00	0.01	Gamma
AE visits patient time use: Nasopharyngitis	1.25	100.00	0.01	Gamma
AE visits patient time use: Back Pain	1.25	100.00	0.01	Gamma
AE visits patient time use: COPD (exacerbation)	24.00	100.00	0.24	Gamma
AE visits patient time use: Diarrhea	1.50	100.00	0.02	Gamma
AE visits patient time use: COVID-19	1.25	100.00	0.01	Gamma

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

Not applicable.

Table 75 Bibliographic databases included in the literature search, N/A

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	N/A	N/A	N/A
Medline	N/A	N/A	N/A
CENTRAL	N/A	N/A	N/A

Abbreviations:

Table 76 Other sources included in the literature search, N/A

Source name	Location/source	Search strategy	Date of search
e.g. NICE	N/A	N/A	N/A
e.g. EMA website	N/A	N/A	N/A

Abbreviations:

Table 77 Conference material included in the literature search, N/A

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	N/A	N/A	N/A	N/A
	N/A	N/A	N/A	N/A

H.1.1 Search strategies

Not applicable.

Table 78 of search strategy table for [name of database], N/A

No.	Query	Results
#1	N/A	N/A
#2	N/A	N/A
#3	N/A	N/A
#4	N/A	N/A
#5	N/A	N/A
#6	N/A	N/A
#7	N/A	N/A
#8	N/A	N/A
#9	N/A	N/A
#10	N/A	N/A

H.1.2 Systematic selection of studies

Not applicable.

Table 79 Inclusion and exclusion criteria used for assessment of studies, N/A

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	N/A	N/A
Intervention	N/A	N/A
Comparators	N/A	N/A
Outcomes	N/A	N/A
Study design/publication type	N/A	N/A
Language restrictions	N/A	N/A

Table 80 Overview of study design for studies included in the analyses, N/A

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Study 1	N/A	N/A	N/A	N/A	N/A	N/A
Study 2	N/A	N/A	N/A	N/A	N/A	N/A

H.1.3 Quality assessment

Not applicable.

H.1.4 Unpublished data

Not applicable.

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

N/A

Table 81 Bibliographic databases included in the literature search, N/A

Database	Platform	Relevant period for the search	Date of search completion
Embase			
Medline			
Specific health economics databases.			

Abbreviations:

Table 82 Other sources included in the literature search, N/A

Source name	Location/source	Search strategy	Date of search

Table 83 Conference material included in the literature search, N/A

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name				

I.1.1 Search strategies

Not applicable.

Table 84 Search strategy for [name of database]

No.	Query	Results
#1		
#2		
#3		
#4		
#5		
#6		
#7		
#8		
#9		
#10		

I.1.2 Quality assessment and generalizability of estimates

N/A

I.1.3 Unpublished data

N/A

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

Not applicable.

J.1.1 Systematic search for studies on excess mortality associated with exacerbations

To identify any published literature that shows the association between exacerbation status and mortality in COPD, we conducted a systematic literature search in MEDLINE via PubMed. All titles and abstracts were reviewed for information that clearly met the inclusion and exclusion criteria presented in Table 86. First-level screening was conducted by two reviewers. The full text of studies that passed the first level of screening was retrieved and reviewed by two reviewers using the same inclusion/exclusion criteria. Any disagreements in terms of relevance were discussed with an independent third reviewer.

Table 85 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
Medline	PubMed	No date limitations applied	11 December 2024

The search strategy used in the search for excess mortality associated with exacerbations are presented in Table 86 and Table 87 presents the search string applied in PubMed.

Table 86 Search strategy for PubMed

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	COPD population	Other diseases 100% Asian population Children
Intervention	No specific intervention specified	None
Comparators	No specific comparator specified	None
Outcomes	Mortality associated with exacerbation status i.e., if the patient has experienced a mild,	Other outcomes not related to survival or mortality associated with exacerbation status e.g., safety or

	moderate or severe exacerbation or if the patient has experienced one or more than one exacerbation	HRQoL outcomes or just survival related to exacerbation and not the nature of the exacerbation or the frequency/number of exacerbations experienced
Study design/publication type	No specific study design preferred but the evidence hierarchy was followed when selecting evidence for the application	None
Language restrictions	English	Other languages

Table 87 Search terms used in PubMed

No.	Query	Results
#1	"pulmonary disease, chronic obstructive"[MeSH Terms] OR "COPD"[Title/Abstract] OR "Chronic Obstructive Lung Disease"[Title/Abstract] OR "Chronic Obstructive Airway Disease"[Title/Abstract] OR "Chronic Airflow Obstruction"[Title/Abstract] OR "Chronic Airflow Limitation"[Title/Abstract]	96,761
#2	"Mortality"[MeSH Terms] OR "Death"[Title/Abstract] OR "Mortality"[Title/Abstract] OR "Fatality"[Title/Abstract] OR "Survival"[Title/Abstract] OR "Survival Rate"[Title/Abstract] OR "survival analys*"[Title/Abstract] OR "Risk of Death"[Title/Abstract] OR "Risk of Mortality"[Title/Abstract] OR "Mortality Risk"[Title/Abstract] OR "Death Risk"[Title/Abstract]	2,978,492
#3	"Exacerbation status"[Title/Abstract] OR "mild exacerbations"[Title/Abstract] OR "moderate exacerbation*"[Title/Abstract] OR "severe exacerbation*"[Title/Abstract]	2,788
#4	#1 AND #2 AND #3	399

39 hits were full-text screened, eight hits were included and 31 were excluded. The excluded hits are presented in Table 88. A PRISMA diagram showing the selection process is presented in Figure 21. As seen, eight studies were included because they showed the association between a COPD patient's exacerbation status and mortality. Of these eight studies, Whittaker et al. 2022 (7) was regarded as most appropriate in terms of modelling the excess mortality associated with exacerbation status in the model but the other seven studies were included as supporting evidence on the association between exacerbation status and mortality. These studies were included as supporting evidence based on dialogue with the DMC who wanted to see evidence on the association between exacerbation status and mortality, thus, we present the evidence we have identified addressing this. The seven supporting studies demonstrating the

association between exacerbation status and mortality are presented briefly in section 8.1.4.2.

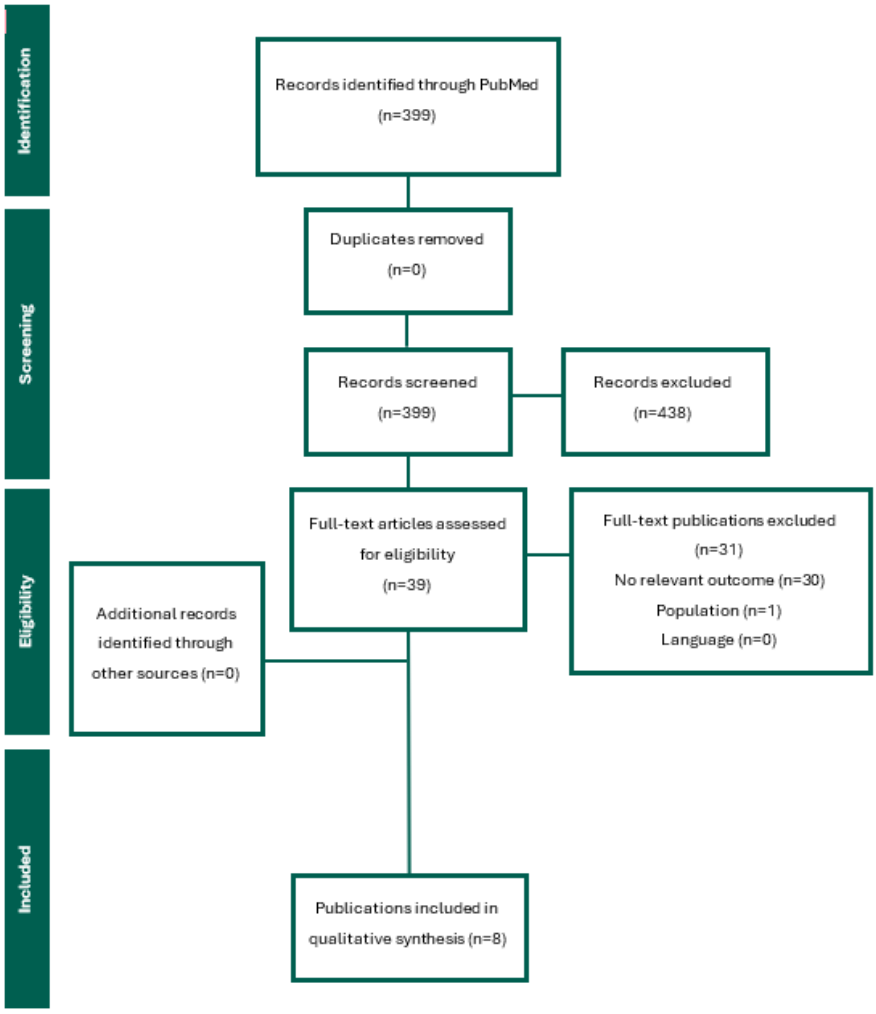


Figure 21: PRISMA diagram for the PubMed search for association between exacerbation status and mortality

Table 88 Hits excluded after full-text screening

Reference	Reason for exclusion
Halpin DM, Miravitlles M, Metzdorf N, Celli B. Impact and prevention of severe exacerbations of COPD: a review of the evidence. Int J Chron Obstruct Pulmon Dis. 2017 Oct 5;12:2891-2908. doi: 10.2147/COPD.S139470. PMID: 29062228; PMCID: PMC5638577.	Only focus on severe exacerbations

Reference	Reason for exclusion
Hurst, J.R., Han, M.K., Singh, B. *et al.* Prognostic risk factors for moderate-to-severe exacerbations in patients with chronic obstructive pulmonary disease: a systematic literature review. *Respir Res* **23**, 213 (2022). https://doi.org/10.1186/s12931-022-02123-5	Does not assess association between mortality and exacerbation status
Daniels K, Lanes S, Tave A, Pollack MF, Mannino DM, Criner G, Neikirk A, Rhodes K, Feigler N, Nordon C. Risk of Death and Cardiovascular Events Following an Exacerbation of COPD: The EXACOS-CV US Study. Int J Chron Obstruct Pulmon Dis. 2024 Jan 18;19:225-241. doi: 10.2147/COPD.S438893. PMID: 38259591; PMCID: PMC10802125.	Does not assess association between mortality and exacerbation status
Bollmeier SG, Hartmann AP. Management of chronic obstructive pulmonary disease: A review focusing on exacerbations. Am J Health Syst Pharm. 2020 Feb 7;77(4):259-268. doi: 10.1093/ajhp/zxz306. PMID: 31930287; PMCID: PMC7005599.	Does not assess association between mortality and exacerbation status
Hawkins NM, Nordon C, Rhodes K, et al. Heightened long-term cardiovascular risks after exacerbation of chronic obstructive pulmonary disease Heart 2024;110:702-709.	Does not assess association between mortality and exacerbation status
Abukhalaf J, Davidson R, Villalobos N, Meek P, Petersen H, Sood A, Tesfaigzi Y, Vazquez Guillamet R. Chronic obstructive pulmonary disease mortality, a competing risk analysis. Clin Respir J. 2018 Nov;12(11):2598-2605. doi: 10.1111/crj.12963. Epub 2018 Oct 25. PMID: 30257066.	Does not assess association between mortality and exacerbation status
Wan ES, DeMeo DL, Hersh CP, Shapiro SD, Rosiello RA, Sama SR, Fuhlbrigge AL, Foreman MG, Silverman EK. Clinical predictors of frequent exacerbations in subjects with severe chronic obstructive pulmonary disease (COPD). Respir Med. 2011 Apr;105(4):588-94. doi: 10.1016/j.rmed.2010.11.015. Epub 2010 Dec 10. PMID: 21145719; PMCID: PMC3046312.	Does not assess association between mortality and exacerbation status
Molinari N, Briand C, Vachier I, Malafaye N, Aubas P, Georgescu V, Roche N, Chanez P, Bourdin A. Hospitalizations for COPD Exacerbations: Trends and Determinants of Death. COPD. 2015;12(6):621-7. doi: 10.3109/15412555.2015.1007931. Epub 2015 Aug 11. PMID: 26263032.	Only focus on severe exacerbations
Golpe R, Figueira-Gonçalves JM, Amado-Diago CA, Expósito-Marrero A, González-Ramos L, Dacal-Rivas D, García-Talavera I, Esteban C. Trajectories of Severe Exacerbations of Chronic Obstructive Pulmonary Disease	Does not assess association between mortality and exacerbation status

Reference	Reason for exclusion
and Their Relationship with Mortality Risk. Lung. 2022 Oct;200(5):601-607. doi: 10.1007/s00408-022-00565-8. Epub 2022 Sep 5. PMID: 36065068.	
Løkke 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 Mar 16;17:569-578. doi: 10.2147/COPD.S344669. PMID: 35321533; PMCID: PMC8937604.	Does not assess association between mortality and exacerbation status
Syndergaard J, Kolte JV, Jørgensen LR, Lindskou TA, Christensen EF, Bøggild H. Prevalence and mortality among patients with COPD hospitalised by ambulance in the 2007-2018 period. Dan Med J. 2022 Oct 20;69(11):A06210526. PMID: 36331155.	Does not assess association between mortality and exacerbation status
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 Mar;37(3):508-15. doi: 10.1183/09031936.00043710. Epub 2010 Jul 1. PMID: 20595157.	Only focus on severe exacerbations
Prognosis of COPD depends on severity of exacerbation history: A population-based analysis. Yunus Colak, Shoaib Afzal, Jacob L. Marott, Børge G. Nordestgaard, Jøgen Vestbo, Truls S. Ingebrigtsen, Peter Lange. Department of Clinical Medicine Clinical Biochemistry	Does not assess association between mortality and exacerbation status
Vogelmeier CF, Rhodes K, Garbe E, Abram M, Halbach M, Müllerová H, Kossack N, Timpel P, Kolb N, Nordon C. Elucidating the risk of cardiopulmonary consequences of an exacerbation of COPD: results of the EXACOS-CV study in Germany. BMJ Open Respir Res. 2024 Mar 30;11(1):e002153. doi: 10.1136/bmjresp-2023-002153. PMID: 38555102; PMCID: PMC10982767.	Does not assess association between mortality and exacerbation status
Casas-Mendez F, Abadías MJ, Yuguero O, Bardés I, Barbé F, de Batlle J. Treatment strategies after acute exacerbations of chronic obstructive pulmonary disease: Impact on mortality. PLoS One. 2018 Dec 14;13(12):e0208847. doi: 10.1371/journal.pone.0208847. PMID: 30550602; PMCID: PMC6294427.	Does not assess association between mortality and exacerbation status
Janson C, Nwaru BI, Wiklund F, Telg G, Ekström M. Management and Risk of Mortality in Patients Hospitalised Due to a First Severe COPD Exacerbation. Int J Chron Obstruct Pulmon Dis. 2020 Oct 28;15:2673-2682. doi: 10.2147/COPD.S276819. PMID: 33149565; PMCID: PMC7604260.	Does not assess association between mortality and exacerbation status

Reference	Reason for exclusion
Whittaker H, Van Ganse E, Dalon F, Nolin M, Marrant-Micallef C, Pison C, Ryan DP, Deslee G, Quint JK, Belhassen M. Differences in severe exacerbations rates and healthcare utilisation in COPD populations in the UK and France. BMJ Open Respir Res. 2022 Aug;9(1):e001150. doi: 10.1136/bmjresp-2021-001150. PMID: 35944943; PMCID: PMC9367183.	Does not assess association between mortality and exacerbation status
Hua JL, Yang ZF, Cheng QJ, Han YP, Li ZT, Dai RR, He BF, Wu YX, Zhang J. Prevention of exacerbation in patients with moderate-to-very severe COPD with the intent to modulate respiratory microbiome: a pilot prospective, multi-center, randomized controlled trial. Front Med (Lausanne). 2024 Jan 5;10:1265544. doi: 10.3389/fmed.2023.1265544. PMID: 38249987; PMCID: PMC10797043.	Does not assess association between mortality and exacerbation status
Aburto M, Esteban C, Moraza FJ, Aguirre U, Egurrola M, Capelastegui A. COPD exacerbation: mortality prognosis factors in a respiratory care unit. Arch Bronconeumol. 2011 Feb;47(2):79-84. English, Spanish. doi: 10.1016/j.arbres.2010.10.012. Epub 2011 Feb 12. PMID: 21316833.	Does not assess association between mortality and exacerbation status
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 Dec;132(6):1748-55. doi: 10.1378/chest.06-3018. Epub 2007 Sep 21. PMID: 17890477.	Only focus on severe exacerbations
Saraiva C, Abreu T, Neves D, Rodrigues F. Mortality Predictive Factors in Subjects With COPD After a Pulmonary Rehabilitation Program: A 3-Year Study. Respir Care. 2016 Sep;61(9):1179-85. doi: 10.4187/respcare.04477. Epub 2016 May 3. PMID: 27143786.	Does not assess association between mortality and exacerbation status
Lin L, Song Q, Cheng W, Li T, Zhang P, Liu C, Li X, Zeng Y, Li X, Liu D, Chen Y, Cai S, Chen P. Impact of exacerbation history on future risk and treatment outcomes in chronic obstructive pulmonary disease patients: A prospective cohort study based on Global Initiative for Chronic Obstructive Lung Disease (GOLD) A and B classifications. J Glob Health. 2024 Oct 11;14:04202. doi: 10.7189/jogh.14.04202. PMID: 39388682; PMCID: PMC11466499.	100% Asian population
Sánta B, Tomisa G, Horváth A, Balázs T, Németh L, Gálffy G. Severe exacerbations and mortality in COPD patients: A retrospective analysis of the database of the Hungarian National Health Insurance Fund. Pulmonology. 2023 Jul-	Does not assess association between mortality and exacerbation status

Reference	Reason for exclusion
Aug;29(4):284-291. doi: 10.1016/j.pulmoe.2022.11.001. Epub 2022 Dec 5. PMID: 36470815.	
Santus P, Di Marco F, Braido F, Contoli M, Corsico AG, Micheletto C, Pelaia G, Radovanovic D, Rogliani P, Saderi L, Scichilone N, Tanzi S, Vella M, Boarino S, Sotgiu G, Solidoro P. Exacerbation Burden in COPD and Occurrence of Mortality in a Cohort of Italian Patients: Results of the Gulp Study. Int J Chron Obstruct Pulmon Dis. 2024 Mar 1;19:607-618. doi: 10.2147/COPD.S446636. PMID: 38444551; PMCID: PMC10913796.	Does not assess association between mortality and exacerbation status
Sun SX, Marynchenko M, Banerjee R, Cheng D, Mocarski M, Yin D, Yu AP, Wu EQ. Cost-effectiveness analysis of roflumilast/tiotropium therapy versus tiotropium monotherapy for treating severe-to-very severe COPD. J Med Econ. 2011;14(6):805-15. doi: 10.3111/13696998.2011.623204. Epub 2011 Oct 12. PMID: 21992217.	Does not assess association between mortality and exacerbation status
Cardoso J, Coelho R, Rocha C, Coelho C, Semedo L, Bugalho Almeida A. Prediction of severe exacerbations and mortality in COPD: the role of exacerbation history and inspiratory capacity/total lung capacity ratio. Int J Chron Obstruct Pulmon Dis. 2018 Apr 5;13:1105-1113. doi: 10.2147/COPD.S155848. PMID: 29670346; PMCID: PMC5896658.	Does not assess association between mortality and exacerbation status
Fortis S, Comellas A, Make BJ, Hersh CP, Bodduluri S, Georgopoulos D, Kim V, Criner GJ, Dransfield MT, Bhatt SP; COPDGene Investigators–Core Units: <italic>Administrative Center</italic>, COPDGene Investigators–Clinical Centers: <italic>Ann Arbor VA</italic>. Combined Forced Expiratory Volume in 1 Second and Forced Vital Capacity Bronchodilator Response, Exacerbations, and Mortality in Chronic Obstructive Pulmonary Disease. Ann Am Thorac Soc. 2019 Jul;16(7):826-835. doi: 10.1513/AnnalsATS.201809-601OC. PMID: 30908927; PMCID: PMC6600841.	Does not assess association between mortality and exacerbation status
Oshagbemi OA, Franssen FME, van Kraaij S, Braeken DCW, Wouters EFM, Maitland-van der Zee AH, Driessen JHM, de Vries F. Blood Eosinophil Counts, Withdrawal of Inhaled Corticosteroids and Risk of COPD Exacerbations and Mortality in the Clinical Practice Research Datalink (CPRD). COPD. 2019 Apr;16(2):152-159. doi: 10.1080/15412555.2019.1608172. Epub 2019 May 23. PMID: 31117850.	Does not assess association between mortality and exacerbation status

Reference	Reason for exclusion
Wedzicha JA, Rabe KF, Martinez FJ, Bredenbröker D, Brose M, Goehring UM, Calverley PMA. Efficacy of roflumilast in the COPD frequent exacerbator phenotype. Chest. 2013 May;143(5):1302-1311. doi: 10.1378/chest.12-1489. PMID: 23117188.	Does not assess association between mortality and exacerbation status
Goossens LM, Leimer I, Metzdorf N, Becker K, Rutten-van Mölken MP. Does the 2013 GOLD classification improve the ability to predict lung function decline, exacerbations and mortality: a post-hoc analysis of the 4-year UPLIFT trial. BMC Pulm Med. 2014 Oct 18;14:163. doi: 10.1186/1471-2466-14-163. PMID: 25326750; PMCID: PMC4223746.	Does not assess association between mortality and exacerbation status
Garcia-Pachon E, Padilla-Navas I. Contribution of Anemia to Multidimensional Indices for Predicting Mortality in Hospitalized Patients With Chronic Obstructive Pulmonary Disease (COPD). Cureus. 2024 Oct 22;16(10):e72126. doi: 10.7759/cureus.72126. PMID: 39575004; PMCID: PMC11580708.	Does not assess association between mortality and exacerbation status

J.1.2 Systematic search for studies on excess mortality associated with COPD stage

To identify any published literature that shows the association between COPD stage and mortality, we conducted a systematic literature search in MEDLINE via PubMed. All titles and abstracts were reviewed for information that clearly met the inclusion and exclusion criteria presented in Table 89. First-level screening was conducted by two reviewers. The full text of studies that passed the first level of screening was retrieved and reviewed by two reviewers using the same inclusion/exclusion criteria. Any disagreements in terms of relevance were discussed with an independent third reviewer.

Table 90 Search string for PubMed

No.	Query	Results
#1	"pulmonary disease, chronic obstructive/mortality"[MeSH Major Topic]	1,440
#2	"Mild COPD"[Title/Abstract] OR "Moderate COPD"[Title/Abstract] OR "Severe COPD"[Title/Abstract] OR "GOLD Stage"[Title/Abstract] OR "GOLD Classification"[Title/Abstract] OR "COPD Severity"[Title/Abstract] OR "COPD Staging"[Title/Abstract]	6,723
#3	#1 AND #2	159

Table 91 Search strategy for PubMed

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	COPD population	Other diseases 100% Asian population Children
Intervention	No specific intervention specified	None
Comparators	No specific comparator specified	None
Outcomes	Mortality associated with COPD stage	Other outcomes not related to survival or mortality associated with COPD stage e.g., safety or HRQoL outcomes
Study design/publication type	No specific study design preferred but the evidence hierarchy was followed when selecting evidence for the application	None
Language restrictions	English	Other languages

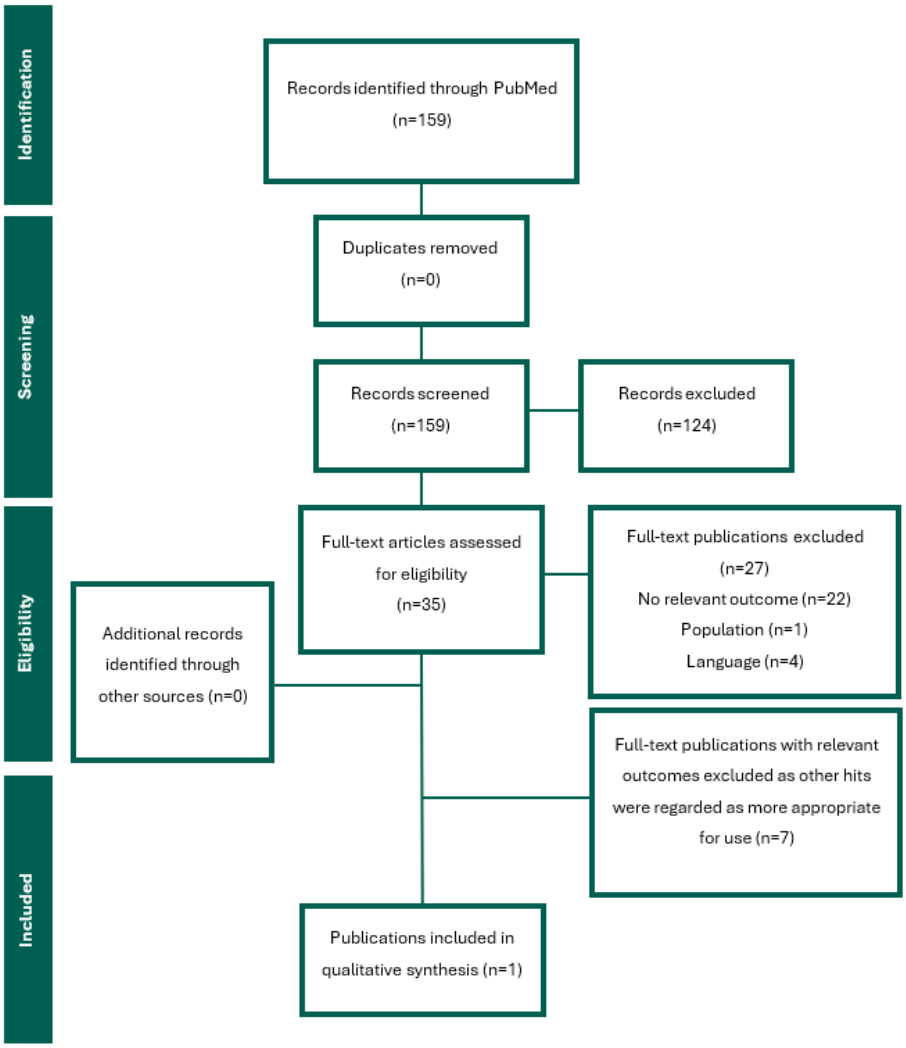


Figure 22: PRISMA diagram for the PubMed search for association between COPD stage and mortality

One hit was included and 34 hits were excluded after full-text screening, and these are presented in **Table** . As seen in **Figure 23**, seven hits had relevant outcomes but were excluded as findings from one hit was regarded as more appropriate to use in the health economic model. All seven hits reported hazard ratios for mortality for different GOLD groups. The study by Shavelle et al. 2009 (50), were included in the health economic analysis to model the excess mortality due to COPD. Shavelle et al. 2009 assessed the life expectancy and the years of life lost due to COPD and the relative risks from this study were applied in the model. The rationale for choosing Shavelle et al. 2009 over the other identified hits with hazard ratios for different GOLD COPD stages and mortality was that the survival of COPD patients was to be compared to the survival of the general population, and SMR was regarded as more appropriate as SMR allows for a direct comparison of observed mortality rates in the COPD population to expected rates based on a standard population. In addition, SMR is a straightforward ratio that is easy to interpret as an SMR greater than 1 indicates higher mortality in the COPD population

compared to the standard population, while an SMR less than 1 indicates lower mortality.

Table 92 Hits excluded after full-text screening

Reference	Reason for exclusion
Berry CE, Wise RA. Mortality in COPD: causes, risk factors, and prevention. COPD. 2010 Oct;7(5):375-82. doi: 10.3109/15412555.2010.510160. PMID: 20854053; PMCID: PMC7273182.	Did not asses mortality associated with COPD GOLD stages
Anzueto A. Impact of exacerbations on COPD. Eur Respir Rev. 2010 Jun;19(116):113-8. doi: 10.1183/09059180.00002610. PMID: 20956179; PMCID: PMC9682573.	Did not asses mortality associated with COPD GOLD stages
Bartolome R. Celli. Predictors of mortality in COPD.Clinics in chest medicine,0272-5231.	Did not asses mortality associated with COPD GOLD stages
Moll M, Qiao D, Regan EA, Hunninghake GM, Make BJ, Tal-Singer R, McGeachie MJ, Castaldi PJ, San Jose Estepar R, Washko GR, Wells JM, LaFon D, Strand M, Bowler RP, Han MK, Vestbo J, Celli B, Calverley P, Crapo J, Silverman EK, Hobbs BD, Cho MH. Machine Learning and Prediction of All-Cause Mortality in COPD. Chest. 2020 Sep;158(3):952-964. doi: 10.1016/j.chest.2020.02.079. Epub 2020 Apr 27. Erratum in: Chest. 2021 May;159(5):2123-2128. doi: 10.1016/j.chest.2021.03.045. PMID: 32353417; PMCID: PMC7478228.	Did not asses mortality associated with COPD GOLD stages
Santibáñez M, Garrastazu R, Ruiz-Nuñez M, Helguera JM, Arenal S, Bonnardeux C, León C, García-Rivero JL. Predictors of Hospitalized Exacerbations and Mortality in Chronic Obstructive Pulmonary Disease. PLoS One. 2016 Jun 30;11(6):e0158727. doi: 10.1371/journal.pone.0158727. PMID: 27362765; PMCID: PMC4928940.	Excluded as Shavelle et al. was deemed more appropriate
Vestbo J, Anderson J, Brook RD, Calverley PM, Celli BR, Crim C, Haumann B, Martinez FJ, Yates J, Newby DE. The Study to Understand Mortality and Morbidity in COPD (SUMMIT) study protocol. Eur Respir J. 2013 May;41(5):1017-22. doi: 10.1183/09031936.00087312. Epub 2012 Sep 27. PMID: 23018908.	Did not asses mortality associated with COPD GOLD stages
COPD staging with GOLD: the newer the better? Boutou, Afroditi K. The Lancet Respiratory Medicine, Volume 3, Issue 6, 418 - 419	Did not asses mortality associated with COPD GOLD stages

Reference	Reason for exclusion
Novotna B, Koblizek V, Zatloukal J, Plutinsky M, Hejduk K, Zbozinkova Z, Jarkovsky J, Sobotik O, Dvorak T, Safranek P. Czech multicenter research database of severe COPD. Int J Chron Obstruct Pulmon Dis. 2014 Nov 10;9:1265-74. doi: 10.2147/COPD.S71828. PMID: 25419124; PMCID: PMC4235208.	Did not asses mortality associated with COPD GOLD stages
Saraiva C, Abreu T, Neves D, Rodrigues F. Mortality Predictive Factors in Subjects With COPD After a Pulmonary Rehabilitation Program: A 3-Year Study. Respir Care. 2016 Sep;61(9):1179-85. doi: 10.4187/respcare.04477. Epub 2016 May 3. PMID: 27143786.	Did not asses mortality associated with COPD GOLD stages
Flynn RWV, MacDonald TM, Chalmers JD, Schembri S. The effect of changes to GOLD severity stage on long term morbidity and mortality in COPD. Respir Res. 2018 Dec 12;19(1):249. doi: 10.1186/s12931-018-0960-3. PMID: 30541559; PMCID: PMC6291946.	Did not asses mortality associated with COPD GOLD stages
Golpe R, Suárez-Valor M, Martín-Robles I, Sanjuán-López P, Cano-Jiménez E, Castro-Añón O, Pérez de Llano LA. Mortality in COPD patients according to clinical phenotypes. Int J Chron Obstruct Pulmon Dis. 2018 May 1;13:1433-1439. doi: 10.2147/COPD.S159834. PMID: 29750029; PMCID: PMC5936010.	Did not asses mortality associated with COPD GOLD stages
Cardoso J, Coelho R, Rocha C, Coelho C, Semedo L, Bugalho Almeida A. Prediction of severe exacerbations and mortality in COPD: the role of exacerbation history and inspiratory capacity/total lung capacity ratio. Int J Chron Obstruct Pulmon Dis. 2018 Apr 5;13:1105-1113. doi: 10.2147/COPD.S155848. PMID: 29670346; PMCID: PMC5896658.	Did not asses mortality associated with COPD GOLD stages
Man SF, Connett JE, Anthonisen NR, Wise RA, Tashkin DP, Sin DD. C-reactive protein and mortality in mild to moderate chronic obstructive pulmonary disease. Thorax. 2006 Oct;61(10):849-53. doi: 10.1136/thx.2006.059808. Epub 2006 May 31. PMID: 16738034; PMCID: PMC2104755.	Did not asses mortality associated with COPD GOLD stages
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 Dec;132(6):1748-55. doi: 10.1378/chest.06-3018. Epub 2007 Sep 21. PMID: 17890477.	Did not asses mortality associated with COPD GOLD stages
Rubinsztajn R, Chazan R. Analiza przyczyn zgonów i chorób współistniejących u hospitalizowanych chorych na przewlekłą obturacyjną chorobę płuc [Mortality and	Article only available in Polish

Reference	Reason for exclusion
comorbidity in hospitalized chronic obstructive pulmonary disease patients]. Pneumonol Alergol Pol. 2011;79(5):343-6. Polish. PMID: 21861258.	
Mattila T, Vasankari T, Kanervisto M, Laitinen T, Impivaara O, Rissanen H, Knekt P, Jousilahti P, Saarelainen S, Puukka P, Heliövaara M. Association between all-cause and cause-specific mortality and the GOLD stages 1-4: A 30-year follow-up among Finnish adults. Respir Med. 2015 Aug;109(8):1012-8. doi: 10.1016/j.rmed.2015.06.002. Epub 2015 Jun 9. PMID: 26108990.	Excluded as Shavelle et al. was deemed more appropriate
Lenoir A, Whittaker H, Gayle A, Jarvis D, Quint JK. Mortality in non-exacerbating COPD: a longitudinal analysis of UK primary care data. Thorax. 2023 Sep;78(9):904-911. doi: 10.1136/thorax-2022-218724. Epub 2022 Nov 24. PMID: 36423926.	Excluded as Shavelle et al. was deemed more appropriate
Dusser D, Wise RA, Dahl R, Anzueto A, Carter K, Fowler A, Calverley PM. Differences in outcomes between GOLD groups in patients with COPD in the TIOSPIR(®) trial. Int J Chron Obstruct Pulmon Dis. 2016 Jan 20;11:133-45. doi: 10.2147/COPD.S97924. PMID: 26855568; PMCID: PMC4725639.	Excluded as Shavelle et al. was deemed more appropriate
Chang C, Yao WZ, Fang TS. [Causes of chronic obstructive pulmonary disease-related death and influencing factors of survival time]. Zhonghua Yi Xue Za Zhi. 2011 Mar 29;91(12):824-7. Chinese. PMID: 21600162.	Article only available in Chinese
Celli B, Decramer M, Kesten S, Liu D, Mehra S, Tashkin DP; UPLIFT Study Investigators. Mortality in the 4-year trial of tiotropium (UPLIFT) in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2009 Nov 15;180(10):948-55. doi: 10.1164/rccm.200906-0876OC. Epub 2009 Sep 3. PMID: 19729663.	Did not asses mortality associated with COPD GOLD stages
Chen CZ, Ou CY, Yu CH, Yang SC, Chang HY, Hsiue TR. Comparison of global initiative for chronic obstructive pulmonary disease 2013 classification and body mass index, airflow obstruction, dyspnea, and exacerbations index in predicting mortality and exacerbations in elderly adults with chronic obstructive pulmonary disease. J Am Geriatr Soc. 2015 Feb;63(2):244-50. doi: 10.1111/jgs.13258. Epub 2015 Feb 2. PMID: 25641518.	Excluded as the population was an Asian population
Conte ME, Pedone C, Forastiere F, Bellia V, Antonelli-Incalzi R. Discriminative and predictive properties of disease-specific and generic health status indexes in elderly COPD patients. BMC Pulm Med. 2008 Aug	Did not asses mortality associated with COPD GOLD stages

Reference	Reason for exclusion
13;8:14. doi: 10.1186/1471-2466-8-14. PMID: 18700955; PMCID: PMC2525624.	
Rhodes, K., Jenkins, M., de Nigris, E. *et al.* Relationship between risk, cumulative burden of exacerbations and mortality in patients with COPD: modelling analysis using data from the ETHOS study. *BMC Med Res Methodol* **22**, 150 (2022). https://doi.org/10.1186/s12874-022-01616-7	Did not asses mortality associated with COPD GOLD stages
Sívori M, Fernández R, Toibaro J, Velásquez Gortaire E. Supervivencia en una cohorte de pacientes con enfermedad pulmonar obstructiva crónica acorde a la clasificación GOLD 2017 [Survival in a cohort of patients with chronic obstructive pulmonary disease according to GOLD 2017 classification]. Medicina (B Aires). 2019;79(1):20-28. Spanish. PMID: 30694185.	Article only available in Spanish
Goossens LM, Leimer I, Metzdorf N, Becker K, Rutten-van Mölken MP. Does the 2013 GOLD classification improve the ability to predict lung function decline, exacerbations and mortality: a post-hoc analysis of the 4-year UPLIFT trial. BMC Pulm Med. 2014 Oct 18;14:163. doi: 10.1186/1471-2466-14-163. PMID: 25326750; PMCID: PMC4223746.	Did not asses mortality associated with COPD GOLD stages
Global Initiative on Obstructive Lung Disease (GOLD) classification of lung disease and mortality: findings from the Atherosclerosis Risk in Communities (ARIC) study.,2006,1,,Respiratory medicine,0954-6111 (Print),100,1,115-22,Mannino DM and Doherty DE and Sonia Buist	Excluded as Shavelle et al. was deemed more appropriate
Soriano Ortiz JB, Almagro P, Sauleda Roig J. Causas de mortalidad en la EPOC [Causes of mortality in COPD]. Arch Bronconeumol. 2009;45 Suppl 4:8-13. Spanish. doi: 10.1016/S0300-2896(09)72857-1. PMID: 20116743.	Did not asses mortality associated with COPD GOLD stages
Goldstein PC. Drawing impairment predicts mortality in severe COPD: a naive approach to COPD mortality prediction. Chest. 2007 Oct;132(4):1411; author reply 1411-2. doi: 10.1378/chest.07-1309. PMID: 17934136.	Did not asses mortality associated with COPD GOLD stages
Hersh CP, DeMeo DL, Al-Ansari E, Carey VJ, Reilly JJ, Ginns LC, Silverman EK. Predictors of survival in severe, early onset COPD. Chest. 2004 Nov;126(5):1443-51. doi: 10.1378/chest.126.5.1443. PMID: 15539711.	Did not asses mortality associated with COPD GOLD stages
Halpin DM, Peterson S, Larsson TP, Calverley PM. Identifying COPD patients at increased risk of mortality: predictive value of clinical study baseline data. Respir Med. 2008 Nov;102(11):1615-24. doi:	Did not asses mortality associated with COPD GOLD stages

Reference	Reason for exclusion
10.1016/j.rmed.2008.05.007. Epub 2008 Aug 8. PMID: 18691861.	
Long-term mortality follow-up of the ISOLDE participants: causes of death during 13 years after trial completion.,2008,10,,Respiratory medicine,1532-3064 (Electronic),102,10,1468-72,Bale G and Martinez-Camblor P and Burge PS and Soriano JB	Did not asses mortality associated with COPD GOLD stages
A 20-year follow-up of a population study-based COPD cohort-report from the obstructive lung disease in Northern Sweden studies.,2009,8,,COPD,1541-2563 (Electronic),6,4,263-71,Lundbäck B and Eriksson B and Lindberg A and Ekerljung L and Muellerova H and Larsson LG and Rönmark	Did not asses mortality associated with COPD GOLD stages
Ekberg-Aronsson, M., Pehrsson, K., Nilsson, JÅ. *et al.* Mortality in GOLD stages of COPD and its dependence on symptoms of chronic bronchitis. *Respir Res* **6**, 98 (2005). https://doi.org/10.1186/1465-9921-6-98	Excluded as Shavelle et al. was deemed more appropriate
Soriano JB, Lamprecht B, Ramírez AS, Martinez-Camblor P, Kaiser B, Alfageme I, Almagro P, Casanova C, Esteban C, Soler-Cataluña JJ, de-Torres JP, Miravitlles M, Celli BR, Marin JM, Puhan MA, Sobradillo P, Lange P, Sternberg AL, Garcia-Aymerich J, Turner AM, Han MK, Langhammer A, Leivseth L, Bakke P, Johannessen A, Roche N, Sin DD. Mortality prediction in chronic obstructive pulmonary disease comparing the GOLD 2007 and 2011 staging systems: a pooled analysis of individual patient data. Lancet Respir Med. 2015 Jun;3(6):443-50. doi: 10.1016/S2213-2600(15)00157-5. Epub 2015 May 17. PMID: 25995071.	Excluded as Shavelle et al. was deemed more appropriate

J.2 Quality assessment

J.2.1 Shavelle et al. 2009

The study by Shavelle et al. (2009) aimed to quantify mortality, examine how it varies with age, sex, and other risk factors, and determine how life expectancy is affected by COPD. The study used data from the Third National Health and Nutrition Examination Survey (NHANES III) and adjusted for age, sex, race, and major medical conditions.

The study classified patients into different stages of COPD based on the GOLD criteria. The study used Kaplan–Meier survival curves and Cox proportional hazards regression models to analyze the data. The Kaplan–Meier survival curves were used to compute the excess death rates (EDRs) associated with different stages of COPD. The Cox proportional

hazards regression models provided hazard ratios for each potential mortality risk factor, including age, sex, race, smoking status, pack-years of cigarette smoking, BMI, major medical conditions, and lung function (COPD) category.

Shavelle et al. 2009 have multiple strengths. The study used a large, nationwide sample as the study used data from NHANES III, a large, nationwide probability sample, which enhances the generalizability of the findings. Also, the study adjusted for multiple potential confounding factors, including age, sex, race, smoking status, pack-years of cigarette smoking, BMI, and major medical conditions. The use of Kaplan–Meier survival curves and Cox proportional hazards regression models adds to the credibility of the findings. The study also had some limitations. As an observational study, it is subject to potential confounding and bias. The study relies on recorded data, which may be subject to recording errors or omissions. In addition, the study does not provide detailed information on how missing data were handled, which could affect the robustness of the findings. The study is based on data from the United States, and there may be differences in healthcare systems, patient demographics, and COPD management practices between the United States and Denmark that could affect the generalizability of the findings to a Danish setting.

In conclusion, the study by Shavelle et al. (2009) appears to be a well-conducted observational study with a robust methodology. Its findings can be valuable for modelling excess mortality associated with COPD GOLD stages in a Danish setting but should be interpreted with caution in the context of potential confounding and bias.

J.2.2 Whittaker et al. 2022

The study by Whittaker et al. (2022) investigates the association between the frequency and severity of COPD exacerbations and subsequent mortality and exacerbation risk. The study uses a large sample size of 340,515 COPD patients, which enhances the statistical power and generalizability of the findings. The study is an observational study that utilizes data from the Clinical Practice Research Datalink (CPRD) Aurum, a primary care database of patients registered at general practices in England. The inclusion criteria for COPD patients are clearly defined, and the study uses validated codes for COPD diagnosis. The exposure of interest, which is the frequency and severity of exacerbations, is identified in the baseline year prior to the index date. The study outcomes, including exacerbations and mortality, are measured between the index date and the end of follow-up.

The study uses Poisson regression to investigate the association between baseline exacerbation frequency/severity and exacerbation events and mortality over follow-up. The study adjusts for multiple confounding factors, including age, gender, smoking status, BMI, depression, anxiety disorder, gastro-oesophageal reflux disease (GORD), lung cancer, myocardial infarction, heart failure, stroke, current asthma, socioeconomic deprivation, mMRC, GOLD-defined lung obstruction, COPD medication use, and blood eosinophil level.

Whittaker et al. 2022 has multiple strengths. The study includes a large cohort of 340,515 COPD patients, which enhances the robustness and generalizability of the

findings. In addition, the use of CPRD Aurum, linked mortality data from the Office for National Statistics (ONS), and secondary care data from Hospital Episode Statistics (HES) provides a comprehensive dataset for analysis. The study provides a granular categorization of exacerbation frequency and severity, which allows for a detailed analysis of their impact on future exacerbations and mortality. Lastly, the study adjusts for a wide range of confounding factors, which helps to isolate the effect of exacerbation frequency and severity on the outcomes.

Whittaker et al. 2022 also has limitations. As an observational study, it is subject to potential confounding and bias. The study relies on recorded data, which may be subject to recording errors or omissions. Although confounders are considered, the study does not control for all potential confounding factors, such as environmental factors or genetic predispositions, which could influence the outcomes. Also, the study is based on data from the UK, and there may be differences in healthcare systems, patient demographics, and COPD management practices between the UK and Denmark that could affect the generalizability of the findings to a Danish setting.

In conclusion, the study by Whittaker et al. (2022) appears to be a well-conducted observational study with a robust methodology. Its findings can be valuable for modelling excess mortality associated with COPD exacerbations in a Danish setting but should be interpreted with caution in the context of potential confounding and bias.

J.2.3 Systematic search for studies on causes of death by lung function in COPD

To identify any published literature ton causes of death (CoD) by lung function in patients with COPD to inform assumptions around the proportion of respiratory causes of death, a systematic literature search in MEDLINE via PubMed was conducted. All titles and abstracts were reviewed for information that clearly met the inclusion and exclusion criteria presented in Table 93. First-level screening was conducted by two reviewers. The full text of studies that passed the first level of screening was retrieved and reviewed by two reviewers using the same inclusion/exclusion criteria. Any disagreements in terms of relevance were discussed with an independent third reviewer.

Table 91 Search string for PubMed

No.	Query	Results
#1	"(((causes of death[Title]) OR (cause specific[Title])) OR (causes[Title]))"	68,305
#2	"(copd[MeSH Terms])"	72,406
#3	"English[Language]"	33,998,566
#4	#1 AND #2 AND #3	199

Table 93 Search strategy for PubMed

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	COPD population	Other diseases
Intervention	No specific intervention specified	None
Comparators	No specific comparator specified	None
Outcomes	Causes of death by lung function	Data not stratified by lung function Other outcomes not related to survival or mortality associated with COPD stage e.g., safety or HRQoL outcomes
Study design/publication type	No specific study design preferred but the evidence hierarchy was followed when selecting evidence for the application	None
Language restrictions	English	Other languages

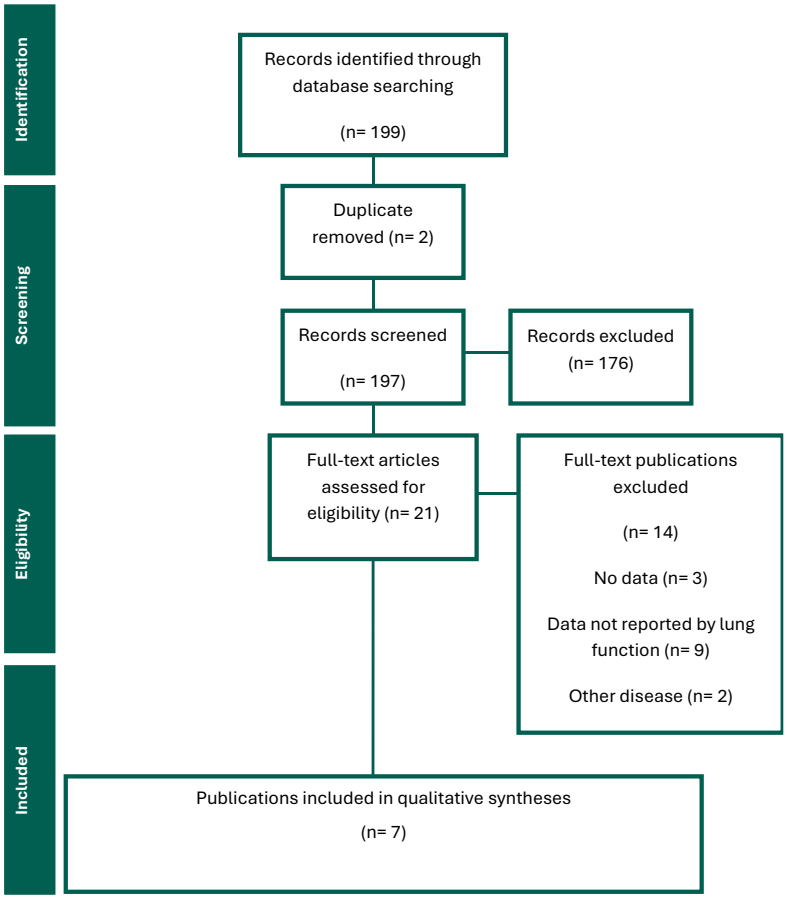


Figure 23: PRISMA diagram for the PubMed search for association between COPD stage and mortality

Seven publications were included and 14 were excluded after full-text screening, and these are presented in **Table** .

Table 94 Hits excluded after full-text screening

Reference	Reason for exclusion
Mettler SK, Sonavane S, Grumley S, Nath HP, Yen AC, Pistenmaa C, Nardelli P, San Jose Estepar R, Cho MH, Diaz AA. Airway-occluding Mucus Plugs and Cause-specific Mortality in Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2024 Jun 15;209(12):1508-1510. doi: 10.1164/rccm.202401-0121LE. PMID: 38771048; PMCID: PMC11208961.	No data

Reference	Reason for exclusion
Wedzicha JA. Causes of Death in Smokers: Implications for Chronic Obstructive Pulmonary Disease Management across Disease Severity. Am J Respir Crit Care Med. 2023 Aug 15;208(4):354-356. doi: 10.1164/rccm.202306-1065ED. PMID: 37429287; PMCID: PMC10449074.	No data
Mackay AJ, Hurst JR. COPD exacerbations: causes, prevention, and treatment. Immunol Allergy Clin North Am. 2013 Feb;33(1):95-115. doi: 10.1016/j.iac.2012.10.006. Epub 2012 Dec 21. PMID: 23337067.	No data
Backman H, Sawalha S, Nilsson U, Hedman L, Stridsman C, Vanfleteren LEGW, Nwaru BI, Stenfors N, Rönmark E, Lindberg A. Cause-Specific Death in Chronic Airway Obstruction and Restrictive Spirometric Pattern. Ann Am Thorac Soc. 2022 Oct;19(10):1783-1787. doi: 10.1513/AnnalsATS.202203-243RL. PMID: 35657669.	Data not stratified by lung function
Soto-Campos JG, Plaza V, Soriano JB, Cabrera-López C, Almonacid-Sánchez C, Vazquez-Oliva R, Serrano J, Ballaz-Quincoces A, Padilla-Galo A, Santos V; Grupo Emergente de Asma (GEA) del Área de Asma de la SEPAR. "Causes of death in asthma, COPD and non-respiratory hospitalized patients: a multicentric study". BMC Pulm Med. 2013 Dec 10;13:73. doi: 10.1186/1471-2466-13-73. PMID: 24321217; PMCID: PMC4029295.	Data not stratified by lung function
Backman H, Sawalha S, Nilsson U, Hedman L, Stridsman C, Vanfleteren LEGW, Nwaru BI, Stenfors N, Rönmark E, Lindberg A. All-cause and cause-specific mortality by spirometric pattern and sex - a population-based cohort study. Ther Adv Respir Dis. 2024 Jan-Dec;18:17534666241232768. doi: 10.1177/17534666241232768. PMID: 38465828; PMCID: PMC10929033.	Data not stratified by lung function
Jensen HH, Godtfredsen NS, Lange P, Vestbo J. Potential misclassification of causes of death from COPD. Eur Respir J. 2006 Oct;28(4):781-5. doi: 10.1183/09031936.06.00152205. Epub 2006 Jun 28. PMID: 16807258.	Data not stratified by lung function
Pływaczewski R, Maciejewski J, Bednarek M, Zieliński J, Górecka D, Śliwiński P. Causes of deaths in COPD patients in primary care setting--a 6-year follow-up. Pneumonol Alergol Pol. 2015;83(3):193-202. doi: 10.5603/PiAP.2015.0031. PMID: 26050979.	Data not stratified by lung function

Reference	Reason for exclusion
Marcon A, Saugo M, Fedeli U. COPD-Related Mortality and Co-morbidities in Northeastern Italy, 2008-2012: A Multiple Causes of Death Analysis. COPD. 2016;13(1):35-41. doi: 10.3109/15412555.2015.1043427. Epub 2015 Sep 14. PMID: 26367073.	Data not stratified by lung function
Pan J, Adab P, Jiang CQ, Zhang WS, Zhu F, Jin YL, Thomas GN, Lam TH. All-cause and cause-specific mortality from restrictive and obstructive spirometric patterns in Chinese adults with and without dyspnea: Guangzhou Biobank Cohort Study. Respir Med. 2019 May;151:66-80. doi: 10.1016/j.rmed.2019.04.002. Epub 2019 Apr 6. PMID: 31047120.	Other disease
Obi J, Mehari A, Gillum R. Mortality Related to Chronic Obstructive Pulmonary Disease and Co-morbidities in the United States, A Multiple Causes of Death Analysis. COPD. 2018 Apr;15(2):200-205. doi: 10.1080/15412555.2018.1454897. Epub 2018 Apr 26. PMID: 29697272.	Data not stratified by lung function
Ma X, Jian S, Hou E, Wei Y, Tu S. Social determinants of health on all-cause and cause-specific mortality in US adults with chronic obstructive pulmonary disease: NHANES 2005-2018. PLoS One. 2025 May 15;20(5):e0322654. doi: 10.1371/journal.pone.0322654. PMID: 40373096; PMCID: PMC12080834.	Data not stratified by lung function
Ekström MP, Wagner P, Ström KE. Trends in cause-specific mortality in oxygen-dependent chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2011 Apr 15;183(8):1032-6. doi: 10.1164/rccm.201010-1704OC. Epub 2011 Jan 7. PMID: 21216882.	Data not stratified by lung function
Cestelli L, Gulsvik A, Johannessen A, Stavem K, Nielsen R. Reduced lung function and cause-specific mortality: A population-based study of Norwegian men followed for 26 years. Respir Med. 2023 Nov-Dec;219:107421. doi: 10.1016/j.rmed.2023.107421. Epub 2023 Sep 29. PMID: 37776914.	Other disease

Included publications

Whittaker et al. 2024

The design of the Whittaker et al. 2024 (54) is described elsewhere. The study was based on the Clinical Practice Research Datalink (CPRD) database where 339,647 people with COPD and managed in primary care settings were included between 1 January 2010 and 1 January 2020. 97,882 people with COPD died during follow-up (25.7% COPD related and 23.3% CV related). Mortality rates per 1,000 patient years were reported and showed a steep gradient between COPD related mortality and airflow limitation. For patients with FEV1 ≥80% adjusted mortality rates were 4.6 and 8.8 respectively for COPD and CVD related mortality. For patients with FEV1 30%-49% adjusted mortality rates were 31.2, 17.4 respectively for COPD and CVD related mortality and for patients with FEV1 <30% the corresponding numbers were 84.4 and 21.8. The study thus demonstrated that the COPD related mortality was below the CVD related mortality for patients with high long function, whereas low lung function was associated with cause of death was COPD that clearly dominated CVD and other causes.

The very large study population and the long follow up in this study means that it should be appropriate to inform about causes of death in a chronic disease like COPD. The fact that all included patients were recruited in primary care settings might suggest that it is less appropriate to inform about CoD in COPD patients in ambulatory settings in Denmark.

Labaki et al. 2023

Labaki et. al 2023 (57) aimed to determine how causes of death varied by lung function impairment in active and former tobacco cigarette users. The study included 10,132 participants and was based on the Genetic Epidemiology of Chronic Obstructive Pulmonary Disease (COPDGene) study. Participants were classified into normal spirometry, PRISm (Preserved Ratio Impaired Spirometry), (GOLD) 1-2 COPD, and GOLD 3-4 COPD. Causes of death were classified by review of death certificates, medical records, and next-of-kin interviews. Over a 10.1-year median follow-up, 2,200 deaths occurred. The study found a steep gradient between lung function and proportion of deaths from respiratory causes, with GOLD 1-2 vs. GOLD 3-4 (incidence rate %, (P value)) 19.8% vs. 61.5% (P<0.001) for respiratory causes, 22.5% vs. 10.1% (P<0.001) for cardiovascular causes and 18.3% vs. 9.3% (P<0.001) for lung cancer.

The very large study population and the long follow up in the COPDGene study suggest that it should be appropriate to inform about causes of death in a chronic disease like COPD. The study is set in US and it is unclear what clinical setting COPD patients were treated.

Bale et al. 2008

Bale et al. 2008 (58) reported based on the Inhaled Steroids in Obstructive Lung Disease (ISOLDE). The study randomised 752 patients with moderate to severe COPD to fluticasone propionate 1000 mcg/day or placebo for three years. Bale and colleagues aimed to investigate the causes of death of the ISOLDE participants up to 13 years post-randomisation based on death certificates. The study used a subsample of 375 participants from the seven ISOLDE original centers where complete extended follow-up was conducted. At 13 years causes of death were; 52% respiratory, 18% cardiac, 14%

lung cancer, 16 (8%) other cancer and 16 (8%) other causes. The study clearly demonstrated that the percentage of respiratory-related deaths increased during the follow-up period; from 46% between0- 3 years, 48% between 3-6 years, 57% between 6-9 years, and 60% between 9-13 years of follow-up (p for trend<0.05).

The small sample size is a clear limitation of the study. However, the long follow up in the ISOLDE trial and the fact that it included moderate to severe COPD suggest it should be appropriate to inform about causes of death in the model on dupilumab. The relatively low mortality after 13 years (56%) in the ISOLDE trial however suggest that the Danish COPD population in ambulatory care relevant for dupilumab has more severe disease.

Mattila et al. 2015

Mattila et al. 2015 (76) set out to study the long-term association between all-cause and cause-specific mortality and GOLD stages 1-4 in a 30-year follow-up among 6,636 Finnish men and women aged 30 or older participating in the Mini-Finland Health Study between 1978 and 1980. CoD was collected from CoD statistics. Adjusted analyses showed that the GOLD stage of the subject had a strong direct relationship with all-cause mortality, mortality from cardiovascular and respiratory diseases, and cancer. At end of follow up 47.7% of all included subjects and 92% of subjects with GOLD stages 2-4 at baseline had died. In total 49.7% of all deaths were classified as cardiovascular causes. In multivariate cox-proportional hazards models HRs for death by respiratory causes GOLD 3 had a HR of 4.95 (95%CI 2.94-8.35) and GOLD 4 had a HR of 15.95 (95%CI 5.77-44.11) – the strongest associations found in the study. Overall the study found that only 16.8% of mortality in subjects with GOLD 2-4 at baseline were respiratory, whereas 46.6% was from cardiovascular causes. The study showed a very clear gradient in all-cause mortality and GOLD stages.

The large sample size and the very long follow up is a clear strength of the study. However, out of 6,636 subjects only 298 had COPD GOLD 2-4 at baseline. The long follow up meant that CoD statistics were obtained in ICD8, 9 and 10 over time can have introduced limitations as also mentioned by the authors. The low number of individuals with COPD GOLD 2-4 limits information that can be extracted to inform mortality assumptions in the model for the Danish setting.

McGarvey et al. 2007

McGarvey et al. 2007 (59) set out to devise systematic methods for ascertainment of cause-specific mortality in COPD based on the TORCH (Towards a Revolution in COPD Health) study. The TORCH study enrolled 6,184 patients with moderate to severe COPD with follow up for 3 years. In the study 875 deaths occurred, but McGarvey et al. includes all 911 deaths recorded for randomized participants. A Clinical Endpoint Committee (CEC) was tasked with categorizing the cause of death and the relationship of deaths to COPD in a systematic, unbiased and independent manner. Of the 911 deaths cause-specific mortality was: cardiovascular 27%, respiratory 35%, cancer 21%, other 10% and unknown 8%. The most common cause of death was respiratory (35%) with approximately 75% occurring after a COPD exacerbation. The CEC was also tasked to

determine if deaths were related to COPD across CoDs and judged that 40% of deaths were “definitely or probably” related to COPD.

The sample size of the study and the number of events is a strength. The fact that the TORCH included moderate to severe COPD as the model does, makes the study relevant. The fact that only 875 of 6,184 (14.2%) were dead after 3 years, suggest that the patient population was less severe compared to the Danish COPD population in ambulatory care relevant for dupilumab and also the patient population included in the ISOLDE trial.

McGarvey et al. 2012

McGarvey et al. 2012 (60) aimed at analyzing the mortality and CoD based on the UPLIFT trial. The trial 5,992 participants with COPD were included in the trial and followed for 4 years and 30 days. A MAC provided systematic, independent and blinded assessment of cause-specific mortality of all 981 reported deaths in the UPLIFT trial. The MAC-assigned causes of death were: respiratory, 35%; cancer, 25%; cardiovascular, 11%; sudden cardiac death, 4.4%; sudden death, 3.4%; other, 8.8%; unknown, 12.4%. The results on CoD were contrasted to those found by the investigators of the trial and in 50.2% there was complete agreement, 18.5% incomplete agreement or 31.3% no agreement. The investigators classified deaths three times more frequently than the MAC. The study also reported CoD by lung function and found that respiratory causes were found in 16.8%, 37.5% and 59.0% in subjects with GOLD 2, 3 and 4 respectively, demonstrating a clear gradient between lung function and respiratory death.

The sample size of the study and the number of events is a strength. The UPLIFT trial included all patients with COPD and differs therefore from the model. The breakdown of cause specific mortality is a strength as and shows a clear gradient between respiratory mortality and lung function. The 4-year follow up not long enough to provide the basis for assumptions around a life-time perspective especially taking into account that only 981 of 5,992 (16.4%) were dead after 3 years.

Berry et al. 2010

Berry et al. 2010 (77) investigates the CoD in COPD by reviewing data from large trials to assess if COPD is underreported as a CoD. They include the TORCH, UPLIFT, EUROSCOP, ISOLDE and LHS III studies that all report causes of death but include participants with varying degree of lung function and tabulates the results by lung function as depicted in Table 95.

Table 96 Causes of Death in COPD – Data from Major Clinical Trials, (#)

Mean FEV_1 (L)	Cardiovascular	Cancer	Respiratory (non-malignant)	Other	Trial	Study Size (n)	Deaths	Study Follow-up
2.75[a]	22%	54%	8%	16%	LHS III	5,887	731	up to 14.5 years

2.54[b]	39%	39%	11%	11%	EUROSCOP	1,277	18	3 years
1.41[a]	32%[c]	32%[c]	22%	13%	ISOLDE	751	68	3 years
1.22[a]	26%	21%	35%	18%	TORCH	6,184	911	3+ years
1.32[a]	16%	22%	39%	23%	UPLIFT	5,993	941	4 years + 30 days

Notes: [a] = post-bronchodilator value, [b] = pre-bronchodilator value, [c] = Percent of deaths attributed to cardiovascular disease (32.4%), cancer (32.4%), and other causes (13.2%) were rounded down numerically in the table. **FEV_1**: Forced Expiratory Volume in 1 second

The table demonstrates how lung function and follow up time alters the CoD for people with COPD, where lower lung function is associated with higher mortality from respiratory causes and subsequently lower rates of cardiovascular and cancer causes. The fact that the reported respiratory mortality in the UPLIFT trial is higher than in the TORCH trial despite the higher lung function could very well be explained by the longer follow-up.

Berry et al. 2010(77) includes patients across large scale trials and as such covers a large population and many events. The study shows a gradient between lung function and respiratory mortality as well as follow up time.

Unpublished data

Not applicable.

J.2.4

Medicinrådet

Danish Medicines Council
Secretariat
Dampfærgevej 21-23, 3rd floor
DK-2100 Copenhagen Ø

+ 45 70 10 36 00
medicinraadet@medicinraadet.dk

www.medicinraadet.dk