Single Technology Appraisal

Dupilumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID6235]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Dupilumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID6235]

Contents:

The following documents are made available to stakeholders:

1. **Company comments on the Draft Guidance**
   a. Company draft guidance response
   b. Company draft guidance response addendum
   c. Company draft guidance response appendices

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Association of Respiratory Nurses
   b. British Thoracic Society
   c. Taskforce for Lung Health and Asthma + Lung UK
   d. NHSE – to follow
   e. Clinical Expert, Richard Russell – to follow

3. **Comments on the Draft Guidance received through the NICE website**

4. **External Assessment Group (EAG) critique of company comments on the Draft Guidance**

5. **Comments following the second committee meeting (ACM2)**
   a. Company comments following ACM2
   b. EAG review of company comments following ACM2
   c. Company response to EAG review
   d. EAG response to company's response to EAG review

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

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

Consultation on the draft guidance document

Draft guidance comments_Sanofi. 16th May 2025.

Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Sanofi
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	None
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Executive summary

We thank the committee for conclusions in the Draft Guidance that recognise the unmet need for COPD patients and the benefits that dupilumab can bring, and the opportunity to respond further to other issues.

Here we have addressed the three key points of uncertainty identified by the committee. We have provided further evidence that shows the economic analysis produces credible and robust modelled outcomes in the population of interest. These are patients with uncontrolled COPD (exacerbating) with Type 2 inflammation (raised blood EOS) who on triple therapy. This patient population is expected to have a higher symptom burden and faster rate of lung function decline, and considerably higher risk for future exacerbations and death, than the 'general' COPD population.

1. Rates of severe exacerbations

Reduction of severe exacerbations with dupilumab treatment would result in a substantial reduction to NHS system resources, in addition to the clinical benefit to patients. (Evidence request 1)

- **Severe exacerbations have a major influence on a patient's disease progression and risk of dying,** due to the direct and permanent impact on the condition of the lungs, making them among the most important clinical events in the lives of COPD patients. It is critical that these events and their associated risks are accounted for appropriately in the economic model. As the committee noted, the EAG approach, turning off direct consideration of severe exacerbations in the form of a case Fatality Rate (CFR), resulted in an unrealistic overestimation of survival.
- **The reduction of severe exacerbations observed in the pooled BOREAS & NOTUS ITT data was 32.6%** (a preplanned analysis), but with a p-value of 0.0725 equating to 93% confidence. We have provided multiple additional analyses to support the validity of the observed 32.6% reduction.
- **We have shown how the absolute reduction in severe exacerbation events observed would be expected to translate into clinical practice and system impact in the NHS**, should dupilumab be prescribed in the population of interest. (**Evidence request 1**)
    - [redacted] bed days avoided per year by year 3 ([redacted]) - much in the winter months
    - [redacted] cost offset by year 3

2. Long-term treatment effect maintenance period of dupilumab

The benefit to FEV1 lung function with dupilumab treatment is rapid and sustained, and these benefits are likely to persist versus SoC. (Evidence request 2)

The assumption of a maintained treatment benefit for dupilumab over the lifetime of the model is supported by its mechanism of action and long-term evidence from other Type 2 inflammatory diseases. By targeting IL-4 and IL-13 signalling, dupilumab addresses a core driver of lung function decline in COPD. This supports the expectation of a sustained benefit in FEV_1 and exacerbation reduction for patients who remain on treatment.

Long-term studies in asthma and atopic dermatitis show that:

- **Clinical benefits are maintained or improve over time**
- **No waning of effect is observed over multiple years**
- **Exacerbation rates continue to decline**, contributing to protection from lung function decline

These trends suggest that the FEV_1 benefit seen in the first three years would likely persist over the long term.

The long-term impact of **smoking cessation** in COPD provides a relevant comparison.

- **Former smokers show early FEV_1 improvement and slower decline**
- **This benefit is preserved for life**, even decades after quitting
- **The trajectory of decline remains lower than in current smokers**

This supports the assumption that **early gains from dupilumab would also be maintained**, with a persistently lower rate of decline compared to standard of care, justifying the model's lifetime treatment effect assumption.

3. Modelling mortality

The BOREAS & NOTUS studies were not powered to assess mortality differences between dupilumab and SoC, but clinical expert opinion confirms that ANY treatment that reduces exacerbations would be expected to reduce the risk of dying, given the strong association between these outcomes. Indeed, a recent real-world study in US COPD patients treated with dupilumab for other indications (ie. where COPD was a comorbid disease), found that all-cause mortality was reduced by 47% compared to matched patients not treated with dupilumab.

As the committee noted, utilising an SMR alone, and therefore turning off any direct impact of exacerbations on mortality, resulted in unrealistic overestimation of modelled survival. The benefit to mortality with dupilumab treatment is primarily based on exacerbation reduction, best captured by a case fatality rate (CFR) for severe exacerbation events. Other causes of COPD mortality are best captured by a standardised mortality ratio (SMR). We have collated and analysed real world mortality for the population of interest to validate the survival outcomes in the modelling using a CFR and an SMR. This shows that together, these appropriately and accurately model the expected mortality for the COPD population of interest.

Real world evidence validates the findings of the economic model. (Evidence request 3)

- We have presented all the available real world data for patient cohorts aligned with the population of interest. Estimated median survival in these datasets is between 6.9 and 8.7 years.
- The updated economic modelling following EAG and Committee 1 preferences provides a median survival estimate of 8.3 years, closely aligned to these real-world estimates.
- In a BOREAS & NOTUS-like population extracted from the English Hospital Episodes Statistics (HES) 39.5% of mortality was due to severe exacerbations vs. 41.5% in the model. **(Evidence request 4)**

Modelling mortality for COPD in the population of interest must include a case fatality rate (CFR) for severe exacerbations, as the core component.

- The association between exacerbations and increased mortality is clear, strong and large.
- Exacerbations are the primary driver for the progressive nature of COPD.
- Clinical expert opinion emphasises that ANY treatment resulting in exacerbation reduction would be expected to also result in mortality reduction.

Modelling approaches using a CFR alone have been explored, importantly capturing severe exacerbation-driven mortality. However, such approaches would overestimate median survival for the population of interest, unless adjusted to also incorporate moderate exacerbation risk.

- Using a CFR alone to model mortality has precedent (e.g., TA461 and literature):

    - The Hoogendorn CFR is optimal as it captures risk from severe exacerbations without arbitrary time limits or inclusion of other COPD-related mortality.
    - We have provided alternative CFR estimates, but these are less suitable as they are for all-cause mortality and use fixed short timeframes for policy or reimbursement purposes (e.g., 90 days). These short durations do not capture full risk, underestimating mortality compared to real-world data. **(Evidence request 6)**
- CFR-only modelling has been further explored **(Evidence request 7)**:
    - Moderate exacerbations also contribute to mortality and evidence implies the risk due to five moderate events may be equivalent to one severe exacerbation.
    - Adjusting the Hoogendorn CFR estimate accordingly suggests a total exacerbation risk of approximately 31%. Median modelled survival is ~6 years without background SMR.
    - With these clinically plausible assumptions, modelled mortality is similar to the updated base case.

Mortality is most appropriately modelled using both the CFR together with a standardised mortality ratio (SMR), capturing both exacerbation risk and general COPD risk. This methodology generates the most credible estimates (Evidence request 5).

- Whittaker 2024 is the best available data providing SMR values because it represents the most up to date published data from an English COPD population.
    - The SMRs in Whittaker 2024 are based on a general COPD based population at lower risk of exacerbations and mortality than the population of interest.
    - For example, the proportion of patients with severe exacerbations at baseline was 4.3% compared to 26.2% observed at baseline in the BOREAS-like population derived from the HES database.
    - The overall mortality rate for the whole population in Whittaker 2024 was 52.4 / 1000 patient years but for patients with no exacerbations at baseline it was only marginally lower at 47.5 / 1000 patient years indicating the low impact of exacerbations on mortality in this population.
    - For comparison the rate calculated from the BOREAS-like population extracted from the HES database was 99.97 / 1000 patient years.
    - Therefore, there is very low risk of double counting the impact of severe exacerbations on mortality in the model by utilising this SMR together with the CFR.

Hoogendorn is the ideal CFR partner for the SMR, as it only captures the excess risk of exacerbations. Other CFR options are for 'All-cause' mortality following a severe exacerbation and their use would introduce double counting for causes of mortality other than severe exacerbations.

Conclusions

We have directed our responses to the key points of uncertainty raised in the draft guidance and have provided additional evidence that supports the validity and appropriate use of the modelling inputs and methodology applied in the company's base case, providing more certainty.

We have shown that real world survival for the population of interest is likely to be between 6.9 and 8.7 years and that the company's modelling approach produces an estimate within this range. We have provided supportive evidence for the use of the modelling methodology, incorporating a CFR and an SMR, and shown how the estimate taken from Hoogendorn for the CFR is credible. There is

also strong reason to believe that the treatment effect of dupilumab should persist whilst on treatment over the lifetime of the model. This is due to exacerbation reduction and suppression of Type 2 inflammation according to the dupilumab mechanism of action and by analogy to TRAVERSE, and to patterns observed in ex-smokers. Furthermore, we have shown that dupilumab does reduce the severe exacerbation rate relative to current SoC and that the impact of this reduction is likely to have significant NHS system benefits in addition to the direct benefits for COPD patients.

We also suggest reconsideration of the issue of health inequalities, with COPD being an identified health inequalities priority of NHS England.

A low willingness to pay (WTP) of £20k/QALY has been suggested in the Draft Guidance due to the uncertainties identified by the committee. We have addressed these points and provided more certainty. Therefore, a more suitable WTP threshold is towards the higher end of NICE's WTP range, given the increased certainty together with the recognised value that dupilumab brings to uncontrolled COPD patients and additional system benefits to the NHS.

Contents

In the Draft Guidance (DG) the committee requested further evidence on the following topics. We have structured our response around these key issues.

1. Evidence to determine whether the magnitude of reduction in severe exacerbations in BOREAS and NOTUS was applicable to clinical practice
2. Evidence to support the company's assumption of a maintained treatment benefit for dupilumab compared with background therapy for the lifetime of the model
3. Data on real-world survival for the population covered by the evaluation to inform the model and validate survival outputs from the model
4. Data estimating how much of the mortality in the population covered by the evaluation is attributable to exacerbations
5. Further evidence to support applying a CFR to account for the increased risk of mortality from exacerbations in addition to the SMRs to estimate mortality associated with COPD severity
6. Alternative sources of evidence for the CFR
7. A scenario analysis applying a CFR due to exacerbations without the application of SMRs, or any other adjustment for mortality
8. Valuing COPD: Willingness to pay
9. Results from the updated model

Responses in detail

1. Evidence to determine whether the magnitude of reduction in severe exacerbations in BOREAS and NOTUS was applicable to clinical practice (Section 3.9 in the Draft Guidance)

In this section we discuss the magnitude of the reduction in severe exacerbations observed in the clinical trials (Section 1.1) and then relate this to the system impact that might be expected across the NHS in England through the introduction of dupilumab. (Section 1.2).

In the studies, severe exacerbation reduction in the ITT had a p-value of **0.0725**, which the EAG noted is close to the conventional significance threshold (**p=0.05**). For patients on treatment for 52 weeks, the p-value improves to **0.0265**. Preventing severe exacerbations is vital but delaying them is also clinically meaningful both are related outcomes; a delay in **time to first severe exacerbation** is statistically significant (**p=0.0160**).

The **COVID-19 pandemic** reduced overall COPD exacerbation rates and clinical experts agreed underreporting of severe cases was likely, as patients avoided hospital visits. A **tipping point analysis** of BOREAS & NOTUS shows that reclassifying just **6 of 698 moderate events** in the SoC arm as severe would yield a statistically significant p-value of **0.045**.

The observed 32.6% reduction in severe exacerbations would have major implications for NHS resource use. If dupilumab were used in the eligible population, it could avoid at least [redacted] bed days, representing a cost offset of £[redacted] million in hospital costs annually (Section 1.2) by year 3.

1.1. Reduction in severe exacerbations observed in the clinical trials

Severe exacerbations have a major impact on a patient's disease progression and risk of dying, making them the most important clinical events in the lives of COPD patients. It is critical that these events and their associated risks are accounted for appropriately in the economic model.

In the pooled BOREAS and NOTUS ITT data, dupilumab reduced severe exacerbations by 32.6%, and the p value associated with this analysis was 0.0725. (Note that analyses of severe exacerbation reduction versus SoC was preplanned in the BOREAS and NOTUS study's Statistical Analysis Plans, individually and pooled, and were not post-hoc assessments as assumed by the EAG) The authors of the pooled analysis publication stated: "Our incidence rate ratio of severe exacerbations with dupilumab is clinically important, albeit not reaching nominal significance, surpassing the reduction seen with inhaled corticosteroid in the IMPACT and ETHOS trials and reduction with long-acting bronchodilators alone."

We note that the EAG have acknowledged that p=0.0725 is very close to the arbitrary threshold for statistical significance (p=0.05), and the 95% CI (0.4 to 1.04) does suggest a strong trend favouring dupilumab for severe exacerbation reduction. The EAG agreed with us that it would not be appropriate to assume no difference in severe exacerbations between treatment arms. The committee also thought it reasonable to assume that dupilumab would result in a reduction in the number of severe exacerbations compared with SoC, but noted this was based on a low number of severe exacerbation events and were concerned that this resulted in a high level of uncertainty.

A summary of the severe exacerbation data including p-values from the pooled BOREAS / NOTUS studies is presented in Table 1 overleaf and discussed in the subsequent paragraph.

Table 1. Summary of the severe exacerbation data from the pooled BOREAS / NOTUS studies

Pooled BOREAS & NOTUS	Outcome	RR or HR vs SoC (CI)	RR vs SoC	P Value
ITT	Moderate or Severe exacerbations	0.687 (0.595 to 0.793)	31.3%	<0.0001
ITT	Moderate Exacerbations	0.689 (0.592 to 0.801)	31.1%	<0.0001
ITT	Severe Exacerbations	0.674 (0.438 to 1.037)	32.6%	0.0725
ITT	Time to first Moderate or Severe Exacerbation	0.770 (0.666 to 0.892)	23.0%	0.0005
ITT	Time to first Moderate Exacerbation	0.747 (0.642 to 0.870)	25.3%	0.0002
ITT	Time to first Severe Exacerbation	0.611 (0.409, 0.912)	38.9%	0.0160
ITT (Tipping point analysis, with 6 more severe events in SoC arm (+10%))	Severe Exacerbations	0.646 (0.422 to 0.991)	35.4%	0.045
mITT (On-treatment period, with an opportunity to reach week 52	Severe Exacerbations	0.581 (0.359 to 0.938)	41.9%	0.0265
mITT (responders, according to model definition)	Severe Exacerbations	[redacted]	[redacted]	<0.0001

ITT: Intention-To-Treat; mITT: Modified Intention-To-Treat; SoC: Standard of Care; RR: Rate Ratio; HR: Hazard Ratio; CI: Confidence Interval

Severe exacerbation events are relatively rare and somewhat stochastic, and as such are not often measured as primary or key secondary endpoints in clinical trials. The committee noted that severe exacerbation rates are expected to be considerably lower within clinical trial settings than that observed in the real world. Individually or pooled, the BOREAS and NOTUS studies were not powered to detect a difference in severe exacerbation rate between the dupilumab and SoC arms. Despite these limitations, the severe exacerbation reduction observed was associated with a p value (p=0.0725), which the EAG have acknowledged is close to the arbitrary threshold for statistical significance of p=0.05. A p-value of 0.0725 holds a 93% statistical confidence that the magnitude of severe exacerbation reduction (32.6%) is true. In the clinical trials for Roflumilast, which is the only other NICE approved medicine for COPD, the reduction in severe exacerbations was 19% in the equivalent raised EOS population and the p-value was 0.3379; resulting in considerably less confidence than the value observed in the BOREAS & NOTUS pooled data.

Given the relatively high level of confidence in the observed BOREAS & NOTUS reduction in severe exacerbations (albeit not statistically significant), it is valid to examine severe exacerbation reduction with dupilumab in alternative ways.

A. Preventing severe exacerbations is key, but delaying them is also clinically important, and these two measurements are related.
    - **In a post-hoc analysis, dupilumab delayed the time to first severe exacerbation compared to SoC by 33%, with a highly significant p value of 0.0005.**
B. As noted above, low severe exacerbation event rates limit the power of clinical trials to detect differences in this outcome. We have reason to believe that the event rate may have been particularly low in BOREAS and NOTUS due to the COVID pandemic environment.

- A substantial reduction in severe exacerbation rate during the pandemic is well documented, proposed to have resulted from a reduction in infection triggers.
- Depending on the population being studied, generally moderate:severe event ratios are expected to be approximately 4:1 (Mittmann, 2008), and in recent studies of populations similar to that of BOREAS and NOTUS, ratios of 2:1 – 5:1 have been described (Pavord, 2021; Criner 2019. However, the moderate:severe ratio in BOREAS and NOTUS was 11:1.
- Clinical experts have suggested that some patients experiencing an exacerbation during the COVID pandemic would have avoided attending the hospital, due to both fears of infection and overburdening stretched NHS services – a view supported by an Asthma UK & the British Lung Foundation patient survey (BLF survey, 2020). Given the definition of moderate and severe exacerbations above, a proportion of otherwise severe exacerbation events are likely to have been recorded only as moderate.
- With an affectedly low severe exacerbation event in the trials due to the pandemic, we have performed additional analyses in which to address this.
  - **We carried out a post-hoc "tipping point" analysis for the purposes of this response. This suggests that if just 6 of 698 moderate exacerbation events in the SoC arm are reclassified as severe, analysis of severe exacerbation reduction would yield a significant p value of 0.045.**
- A more appropriate population from which to calculate the reduction in severe exacerbation is the cohort with an '*opportunity to reach 52 weeks'.* Severe exacerbations are rare events, and so it is important to derive an AER from patients with the fullest possible record of treatment in order not to skew the analysis. The studies were designed with an end point at 52 weeks but the NOTUS interim analysis (which is the final analysis) resulted in approximately 20% of patients not completing 52 weeks of treatment. Therefore, we have extracted the population with an '*opportunity to reach 52 weeks'* from the pooled BOREAS and NOTUS studies.
- A proportion of patients in the dupilumab arm discontinued treatment during the study period and switched to SoC. This is true of patients in both the *modified ITT* and ITT populations alike. Exacerbations recorded over 52 weeks for such patients may therefore be partly ascribed to dupilumab and partly to SoC therapy. To appropriately understand severe exacerbations in dupilumab versus SoC treated patients, use of an "on-treatment" population is appropriate. This is the modified ITT population with an 'opportunity to reach week 52 whilst on treatment'.
  - **A post-hoc analysis of the modified ITT in which all patients had an opportunity to reach week 52 and were still on initial treatment at that time (88.6% of the ITT), resulted in severe exacerbation reduction with a significant p value of 0.0265.**
- In the real world, only patients who respond to treatment continue treatment. Patients who do not respond to dupilumab would return to SoC alone. The economic model includes a responder criterion for continued treatment at week 52, that would likely be applied in clinical practice.
  - **In patients meeting the model responder criterion at week 52 the p-value for severe exacerbation reduction is <0.0001.**

C. Adjudication of exacerbation events as "moderate" or "severe" is made based on the treatment setting, where a moderate exacerbation becomes a severe exacerbation upon patient hospitalisation. With this context, clinical experts agree that both moderate and severe exacerbations are driven by the same triggers and biology, and therefore it is

generally observed in trials and real-world that a medication-driven reduction in moderate exacerbations also results in a similar magnitude of severe exacerbation reduction.

- **In BOREAS and NOTUS there was a similar magnitude of reduction achieved for both moderate (31.1% - p<0.0001) and severe (32.6% - p=0.0725) exacerbations, consistent with clinical expert opinion. The statistically significant reduction in moderate exacerbations supports confidence in a material reduction also for severe exacerbations.**

1.2. Clinical Relevance of Severe Exacerbation Reduction in UK Practice

The reduction in severe exacerbations observed in the BOREAS and NOTUS trials is directly applicable to UK clinical practice and holds meaningful implications for both patient outcomes and NHS resource use. In the pooled data from BOREAS and NOTUS, treatment resulted in a 32.6% relative reduction in severe exacerbations compared with SoC. This benefit was demonstrated in the population of interest.

In real-world UK settings, the baseline rate of severe exacerbations for the population of interest is approximately 0.41 events per patient per year (Appendix A), with each event typically resulting in hospital admission and an average length of stay of 2.9 days. Applying the trial-based relative reduction to this baseline suggests an absolute reduction of 0.13 severe exacerbations per patient annually.

This reduction has clear and significant implications for NHS resource use. Under full uptake of dupilumab for eligible patients, preventing over 4,300 severe exacerbations in Year 1 alone would avoid an estimated 12,708 hospital bed days. Financially, this translates to annual cost savings of more than £11 million, using a conservative estimate of £926.02 per day as per the 2023/24 national schedule of NHS COPD hospital admission cost. These reductions in hospitalisations would be particularly valuable given the persistent bed capacity constraints facing the NHS, especially during periods of peak demand such as occur in Winter. Freeing up bed capacity reduces the blockages caused by restrictive inpatient availability, helping to streamline patient flow from admission through to discharge. As highlighted in The Health Foundation report 2024, between 21,000 and 37,000 additional beds may be needed in England by 2030 to maintain 2018/19 levels of care. However, part of this gap could be addressed by improving system efficiency and reducing delays—doing "things faster." Avoiding exacerbation driven admissions in COPD, enabling more timely movement through the care pathway and supporting more effective discharge processes.

Table 2: Estimated UK Impact of Severe Exacerbation Reduction with 100% uptake (full eligible population)

Scenario	**Year 1**	**Year 2**	**Year 3**
Eligible population	33,292	33,625	33,932
Market share uptake (%)	100%	100%	100%
Treated patients	33,292	33,625	33,932
Severe exacerbations avoided	4382	4426	4466
Hospital bed days saved	**12,708**	**12,835**	**12,952**
Total estimated annual cost savings	£11,767,460	£11,885,242	£11,993,753

Table 3: Estimated UK Impact of Severe Exacerbation Reduction with projected market share uptake

Scenario	**Year 1**	**Year 2**	**Year 3**
Eligible population	33,292	33,625	33,932
Market share uptake (%)	[redacted]	[redacted]	[redacted]

Treated patients		[redacted]			[redacted]			[redacted]	
Severe exacerbations avoided		[redacted]			[redacted]			[redacted]	
Hospital bed days saved		[redacted]			[redacted]			[redacted]	
Total estimated annual cost savings		[redacted]			[redacted]			[redacted]	

A complementary approach is to consider the NHS impact at the local level. One COPD consultant that we spoke to highlighted that in his hospitals there are approximately 150 beds across four respiratory wards, and these beds are always full. Indeed, the hospital is so busy, there are usually respiratory patients who are in need but unable to access beds. On average about 50-75 of these beds are occupied with COPD patients suffering from exacerbations.

He believed the reduction of exacerbations observed in the BOREAS & NOTUS clinical trials would make a very meaningful change to their current clinical practice. He calculated that if there are on average 50 COPD patients in hospital beds with an exacerbation, then a 30% reduction in severe exacerbations would equate to 15 beds becoming available every day. Over a year this is 5,475 bed days saved.

This is likely to be an overestimate, as not all patients will have T2 inflammation and full uptake in the eligible population is unlikely to occur. A more realistic estimate might be as follows. Around 40% of patients have Type 2 inflammation and in the NICE BIT [redacted] uptake is assumed at year 3. Applying these constraints the numbers above it is not unreasonable to assume that [redacted] bed days per year could be avoided in that local setting alone ([redacted]), equating to [redacted] in avoided costs. This would have a significant positive impact on local budget, capacity and patient flow.

1.3. Conclusion

Overall, we have provided additional compelling evidence and clinical expert opinion for accepting that there is a material difference in severe exacerbations between dupilumab and SoC, and that the magnitude of difference is most likely that observed in the pooled BOREAS and NOTUS ITT data (32.6% reduction versus SoC). This data reduces uncertainty in the magnitude of benefit observed in BOREAS & NOTUS.

We have shown that the system level impact of introducing dupilumab for the treatment of COPD could be substantial, particularly in the winter months when exacerbations are most likely to occur and pressure on inpatient respiratory admissions is at its highest.

2. Evidence to support the company's assumption of a maintained treatment benefit for dupilumab compared with background therapy for the lifetime of the model. (Section 3.10 in the Draft Guidance)

In this section we discuss the applicability of the asthma dupilumab TRAVERSE findings to inform FEV1 maintenance in COPD and provide additional requested analyses (Section 1.1), and then provide rationale for the expected persistence of benefit throughout the lifetime of the model (Section 1.2).

Lung function decline is accelerated in COPD, especially when Type 2 inflammation is present. This is a modifiable factor targeted by dupilumab. In BOREAS and NOTUS, dupilumab showed rapid and sustained FEV1 improvement, and the long-term asthma data from TRAVERSE supports continued benefit of up to three years, with no evidence of waning over this time.

Shared mechanisms of action for dupilumab between asthma and COPD, such as reduction in mucus plugging and decrease in airway restriction and resistance justify using this asthma data to model COPD outcomes. While EAG noted demographic differences between asthma and COPD populations, matched population adjustments for age, baseline FEV1, and comorbidities show no impact on the ability of dupilumab to maintain FEV1 benefits for up to 3 years, indicating the effect is consistent regardless of differences between asthma and COPD trial populations.

Long term studies in other dupilumab indications do not show waning of treatment effect (up to five years in the case of atopic dermatitis). Data on smoking cessation in COPD, **demonstrates that FEV1 improves after stopping smoking and then declines more slowly than in current smokers**. Importantly, this benefit persists long-term without waning, as former smokers do not revert to the faster decline seen in active smokers. By analogy it is not expected that the relative FEV1 benefit vs SoC would decline; indeed, the relative benefit might increase over time.

2.1. TRAVERSE data informs the maintenance of FEV1 benefit with dupilumab

Lung function decline is an expected part of the ageing process. However, even studies of people with no chronic respiratory disease indicate that a risk factor for an increased rate of decline is the presence of Type 2 inflammation, suggesting that some components of decline may not be "normal". These components associated with Type 2 inflammation are likely to be modifiable by treatments that effectively target Type 2 inflammation, such as dupilumab, and this treatment effect would be expected to continue with long-term treatment. Additionally, COPD results in more rapid decline than the nonpatient age-matched population, and COPD with Type 2 inflammation has more rapid decline again. This was agreed by the committee during the first appraisal meeting.

In the BOREAS and NOTUS studies, dupilumab treatment resulted in a rapid (within 1 week) and substantial (83ml over and above SoC) improvement in FEV1, that was then sustained through the 52-week study period. In the absence of data for long-term treatment of COPD with dupilumab, it is reasonable and appropriate to utilise data based on long-term treatment of moderate-severe asthma with dupilumab, from the TRAVERSE open-label extension study, as a proxy to model the expected effect in COPD patients. The relevance of this methodology is supported by two underlying principles:

1. COPD and asthma individually are differentiated chronic respiratory diseases, but the mechanisms of lung function decline are broadly similar for the Type 2 subsets of both COPD and asthma

2. The mechanisms of action for dupilumab in the Type 2-inflamed lung are to reduce mucus plugging, decrease airway restriction and resistance, and increase airway volume, as demonstrated in the dupilumab VESTIGE study.

We note that the EAG agreed that the FEV1 treatment effect for dupilumab patients continuing treatment would likely persist for a period post study, and included it in their base case, and that their clinical experts agreed the TRAVERSE data is a good proxy and the best available evidence to model an extended period of lung function maintenance after the end of the trial.

Dupilumab is indicated for the treatment of multiple diseases which are driven by underlying Type 2 inflammation. Data from both long-term prospective studies and RWE indicate that the benefits provided by dupilumab treatment are maintained and often incrementally improved by continued long-term treatment – there is no overall indication of a "waning" in treatment effect. In particular, patients followed from phase 2 and 3 moderate-severe asthma studies though to the TRAVERSE open-label extension (in which patients were treated for up to 3 years with dupilumab), demonstrated that initial improvements in FEV1 were maintained up until the end of the study. We point out that the COPD model limits the applied FEV1 maintenance period up until the point where TRAVERSE data finishes (3 years) – but otherwise, TRAVERSE shows no indication that maintenance of FEV1 would not continue beyond this point.

Lung function decline in both asthma and COPD is associated with common mechanisms including airway wall remodelling, altered airway compliance, and mucus hypersecretion (Ramos, 2014; Newby, 2014) – all associated with Type 2 inflammation. (Emphysema is a driver of lung function decline only in a proportion of COPD patients). By targeting Type 2 cytokine signalling by IL-4 and IL-13, evidence indicates that dupilumab positively impacts lung function by reducing fibrosis and airway thickening (airway remodelling), reducing airway contractility (airway compliance) and airway resistance and reducing air trapping associated with mucus plugs. Indeed, the recently published VESTIGE study of dupilumab versus placebo in the treatment of asthma quantified reduced airway inflammation and mucus plugging, leading to improved airway volume and flow.(Wechsler 2022) Such benefits may be considered part of the "mechanism of action" of dupilumab in lungs under the influence of chronic Type 2 inflammation, and would be reasonably postulated to be applicable to the treatment of both asthma and COPD when Type 2 inflammation is present.

Additionally, an exploratory investigation of lung function in the asthma QUEST study, where the trajectory of FEV_1 from week 4 to 52 was measured (excluding the initial improvement in FEV_1), suggested that, while placebo treated patient's lung function decreased by approximately 40 mL over a year, those patients treated with dupilumab experienced no decrease (Castro 2018). This reported dupilumab protection from lung function decline in asthma patients lends support to the hypothesis that dupilumab treatment can result in extended period of lung function maintenance and is being investigated further in the long-term phase 4 ATLAS study.

The EAG have noted that the clinical characteristics and demographics of patients in the asthma TRAVERSE study were different, and their clinical experts suggested that differences in age, baseline FEV1 and comorbidities may be factors that limit the applicability of this data to the COPD population in BOREAS and NOTUS.

1. Age is an important covariate to consider, given the association of lung function decline with age.
2. The starting FEV1 level could conceivably have an impact on lung function decline. However, when observing the relative rate of decline for COPD patients (rather than absolute volume),

a more steady rate is observed between the ages of 40 and 70. We therefore disagree with the EAG expert clinical opinion that the rate is higher in more mild disease, particularly if assessed more appropriately as a rate decrease in % predicted FEV1.

- One study helpfully measured % predicted FEV1 decreases for COPD patients broken down by GOLD levels of severity (Tantucci 2012). Here, the largest proportional decrease was observed for moderate patients, and the largest magnitude decreases were observed in moderate and severe patients.
- Additionally, Fenwick (2021) has calculated transition probabilities for patients moving from mild (FEV_1 ≥80%) to moderate (FEV_1 50-79%) to severe (FEV_1 30-49%) to very severe (FEV_1 <30%), used to inform progressive disease in the economic model. Patients move from mild to moderate and moderate to severe at similar rates, and the transition rate is higher from severe to very severe.

3. Comorbidities are more common in COPD patients than asthma, with cardiovascular (CV) disease prominent. There is an association between lung function decline and CV, however clinical experts have advised that mechanistically it is poor lung function that likely drives CV disease, and not vice versa.

An exploratory matching exercise using the Matching Adjusted Indirect Comparisons (MAICs) methodology was carried out on TRAVERSE data. To ensure comparability of the asthma and COPD populations at baseline, age and pre-BD FEV1 were weighted in the TRAVERSE population to match to the baseline characteristics of the pooled BOREAS and NOTUS studies (by both mean and standard deviation). Despite comorbidities being unlikely to influence lung function decline, we have also matched by classification of comorbidities (cardiac disorders, vascular disorders and respiratory disorders). Pertinent patient characteristics of these populations are summarised in Table 4 below:

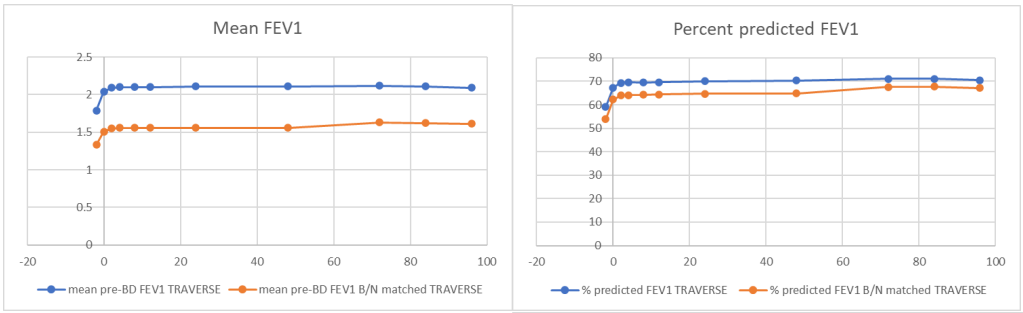
Table 4. Comparison of the Pooled BOREAS and NOTUS, TRAVERSE before and after matching on age and pre-BD FEV1 (A), on age, pre-BD FEV1 and cardiac disorder comorbidities (B), on age, pre-BD FEV1 and vascular disorder comorbidities (C), on age, pre-BD FEV1 and respiratory etc disorder comorbidities (D).

Baseline Characteristics	**Pooled BOREAS and NOTUS**	**TRAVERSE**	**A. TRAVERSE, matching on age (Mean 65.1 y, SD=8.2) and pre-BD FEV1 (Mean 1.33L, SD = 0.48)**	**B. TRAVERSE, matching on age (Mean 65.1 y, SD=8.2) and pre-BD FEV1 (Mean 1.33L, SD = 0.48) plus 25.7% cardiac disorders**	**C. TRAVERSE, matching on age (Mean 65.1 y, SD=8.2) and pre-BD FEV1 (Mean 1.33L, SD = 0.48) plus 60.8% vascular disorders**	**D. TRAVERSE, matching on age (Mean 65.1 y, SD=8.2) and pre-BD FEV1 (Mean 1.33L, SD = 0.48) plus 13.0% respiratory etc disorders**
Mean Age (years)	65.1	48.4	65.1	65.1	65.1	65.1
Male (%)	66.8	37.8	32.3	34.5	32.4	32.2
Female (%)	33.2	62.1	67.7	65.5	67.6	67.8
Mean BMI (kg/m2)	27.8	29.0	29.0	29.2	29.2	29.0
Mean pre-BD FEV1 (L)	1.33	1.79	1.33	1.33	1.33	1.3
Mean Blood EOS (giga/L)	0.40	0.36	0.34	0.34	0.34	0.3
Effective Sample size (ESS)		2062	533	489	528	533

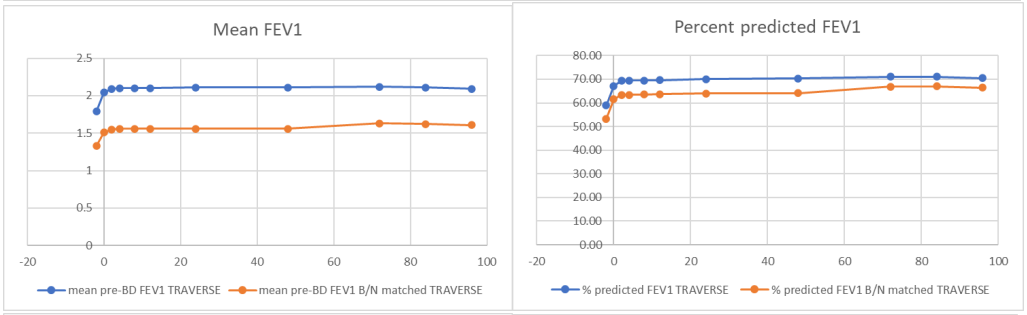
FEV1 maintenance over time, measured as either absolute mean FEV1 or relative percent predicted %, from 0 to 96 weeks of the TRAVERSE study (following the 52 weeks of parental studies) for different MAIC populations, are represented below in Figure 1.

Figure 1 Mean pre-bronchodilator FEV1 and percent predicted pre-bronchodilator FEV1 measurements in the TRAVERSE study, for MAIC populations matched on age and pre-BD FEV1 (A), on age, pre-BD FEV1 and cardiac disorder comorbidities (B), on age, pre-BD FEV1 and vascular disorder comorbidities (C), on age, pre-BD FEV1 and respiratory etc disorder comorbidities (D).

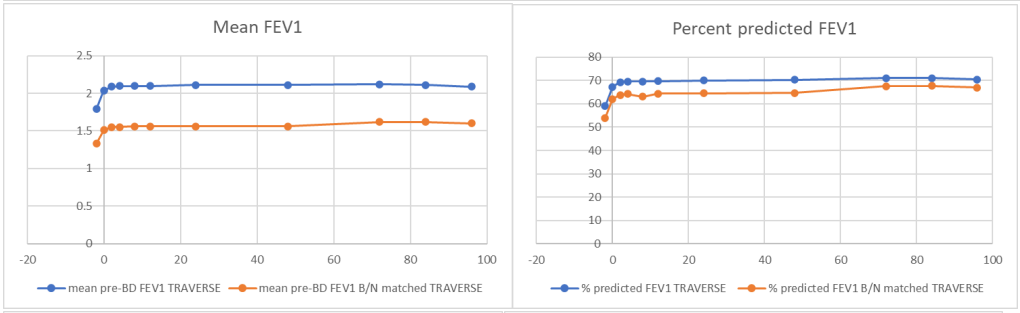
A.



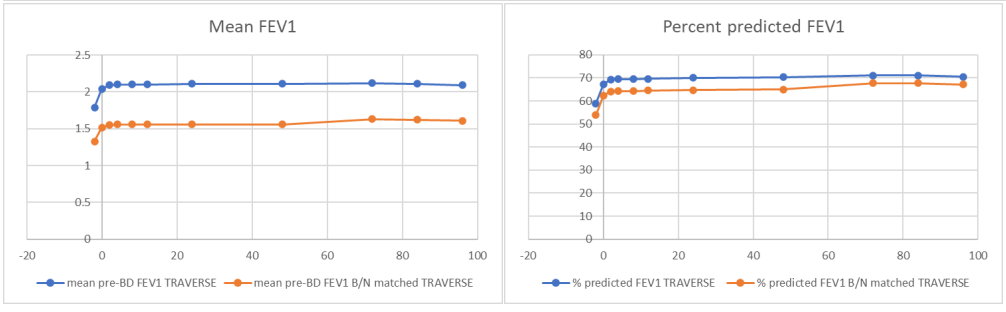
B.



C.



D.



In our response to the EAG clarification questions, we had already provided the populations matched on age and FEV1. Figure 1 also shows that FEV1 is maintained in matched populations considering also cardiac, vascular and other respiratory comorbidities. These data show that matched population adjustments to age, baseline FEV1 and comorbidity class have had no impact on the ability of dupilumab treatment to maintain FEV1 benefit up to 3 years. This maintenance effect is not dependent on patient factors that may be different between COPD and asthma trial populations.

The NICE committee acknowledged the lack of long-term data for dupilumab in people with COPD on which to estimate the long-term treatment effect and agreed in the absence of evidence it is reasonable to base this on TRAVERSE. We have shown above that the pathophysiology of lung function decline (and particularly that associated with Type 2 inflammation), the mechanism of dupilumab in the Type 2 inflamed lung and the demonstration of FEV1 benefit maintenance the TRAVERSE study (matched by patient characteristics to BOREAS & NOTUS), mean that it is appropriate to model a 3 year FEV1 maintenance for patients continuing dupilumab treatment.

2.2 The expected persistence of FEV1 benefit with dupilumab

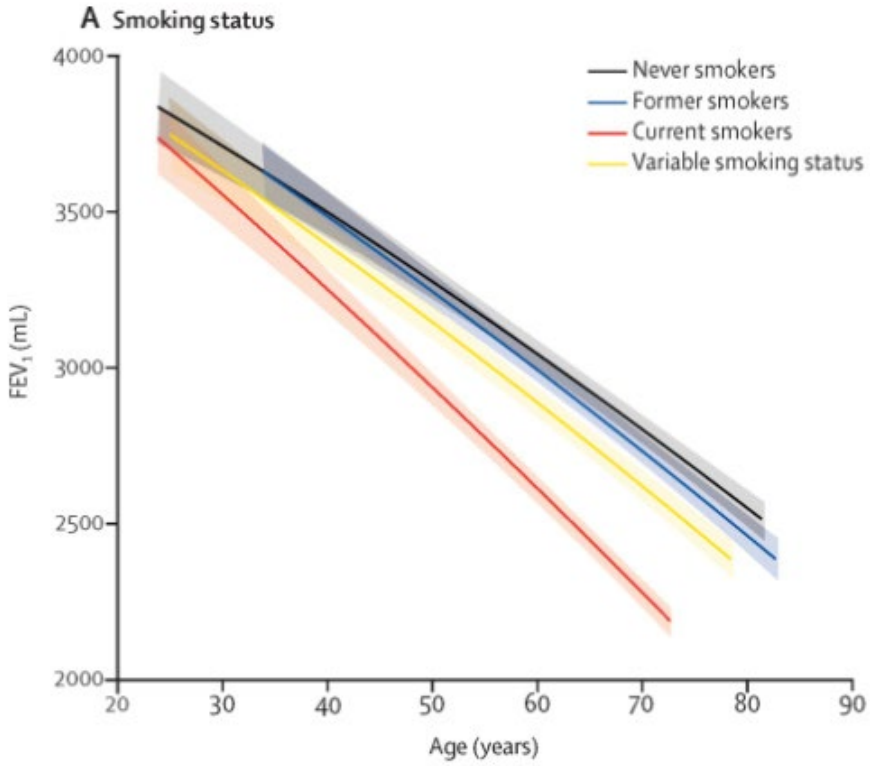
The NICE committee recalled that after the 3-year treatment effect maintenance period, the same transition probabilities between COPD health states as for background therapy are applied. And because of the higher FEV1 for people in the dupilumab arm at 3 years, a treatment effect is maintained throughout the lifetime of the model (while people remain on dupilumab).

It is appropriate to assume that a continued delta in FEV1 lung function between dupilumab and SoC would be maintained throughout the lifetime of the model for the following reasons:

1. TRAVERSE data (as above) did not indicate any waning of FEV1 maintenance at 3 years, suggesting that it may well be expected to continue beyond this time.
2. Long-term studies of dupilumab efficacy in other indications has in each case demonstrated continued, and often incrementally improved, efficacy over time.
    a. Dupilumab is a precision medicine specifically inhibiting Type 2 inflammation
    b. TRAVERSE also demonstrated that the exacerbation rate continued to decrease incrementally from year 1 to year 3 (Wechsler 2022).
    c. Continual dupilumab treatment of atopic dermatitis, for 4 additional years in an open label extension study that followed on from other clinical trials, resulted in a mean of the key Eczema Area and Severity Index (EASI) score of 3.15 at 52 weeks and 2.46 at 204 weeks (versus 32.25 at baseline) (Beck, 2022)
3. The FEV1 rate of decline is faster in patients with Type 2 inflammation (section 3.8 of the Draft Guidance). Inhibiting Type 2 inflammation might be expected to decrease this rate, in comparison to patients on SoC.
4. The expected long-term exacerbation reduction with dupilumab would be expected to achieve a cumulative protection from the lung damage caused by exacerbations, versus SoC

A UK clinical expert we spoke to recently pointed to data that may usefully describe a similar situation, which considers the long-term consequences of smoking cessation in COPD patients over time, as analogy to long-term dupilumab treatment. Smoking cessation results in a magnitude improvement of FEV1 over a moderate time frame. If the former smoker continues to abstain, their FEV1 declines at a rate significantly lower than that for current smokers. Crucially in the longer term patients do not lose the benefit of smoking cessation by developing a faster decline, as if they were again smoking (i.e. no waning of the benefits of smoking cessation would be expected). This is illustrated in the recent study by Oelsner. See Figure 2 overleaf (Oelsner 2020).

Figure 2. Long term FEV1 benefits of smoking cessation (Reproduced from Oelsner 2020).



Taken together, the points above suggest that the delta between dupilumab and SoC would be expected to be maintained or indeed increase over an extended period, for patients remaining on treatment (i.e. the rate of lung function decline for dupilumab is likely to be slower than that for SoC due to the lower rate of exacerbations). The company base case therefore provides a credible estimate for disease trajectory, with both dupilumab and SoC patients following the same underlying FEV1 transition probabilities with adjustment for exacerbations from the 3-year point for the lifetime of the model.

3. Data on real-world survival for the population covered by the evaluation to inform the model and validate survival outputs from the model (Section 3.11 in the Draft Guidance)

In this section we discuss real-world evidence suggestive of a mortality benefit for COPD patients treated with dupilumab (Section 3.1), the impact on mortality of exacerbations (Section 3.2), provide a correction to the presentation of the median survival estimates (Section 3.3) and present further evidence to support the modelled survival outcomes from several real world sources (Section 3.4)

We have gathered further **real-world evidence matching as closely as possible to the population of interest** to validate the median survival predicted by the economic model. This evidence comes from three key real world sources we have developed (English HES, French SNDS and US claims data) and is also supported by published literature.

Estimated **median survival in these datasets is between 6.9 and 8.7 years**. This validates the updated economic modelling following EAG and Committee 1 preferences which predicts approximately 8 years.

COPD significantly increases mortality risk due to exacerbations that cause lasting lung damage and trigger cardiovascular complications, and raise the risk of future exacerbations, compounding mortality over time. Data from the IMPACT and ETHOS studies suggest a direct link between exacerbation frequency and mortality, underscoring the importance of preventing exacerbations to improve long-term outcomes including risk of mortality.

3.1. Reduction in mortality with dupilumab treatment

The BOREAS & NOTUS studies were not powered to assess mortality differences between dupilumab and SoC, and consequently there is no direct evidence from these studies for a reduction in mortality with dupilumab treatment. However, a recent real-world study in US COPD patients treated with dupilumab for other indications (ie. where COPD was a comorbid disease), found that all-cause mortality was reduced by 47% compared to matched patients not treated with dupilumab (Sun 2024).

1521 COPD patients treated with dupilumab for a median follow-up period of 80.1 weeks were compared to propensity score-matched on baseline characteristics to a non-treated cohort. Patients in this cohort may have been prescribed dupilumab for atopic dermatitis, prurigo nodularis, chronic rhinosinusitis with nasal polyps or eosinophilic esophagitis. These are conditions that do not carry a substantially increased mortality risk.

Dupilumab was associated with significantly lower risk of all-cause mortality (0.53 [95% CI = 0.43-0.65], $p < 0.001$).

Sun 2024 was not a Sanofi sponsored study. Whilst the mean baseline absolute blood eosinophil count after matching was approximately 0.6 to 0.73 $10^3/\mu L$ in both arms indicating Type 2 disease, the population was defined differently to the BOREAS and NOTUS populations and so the study outcomes should be treated with caution. The authors themselves state that the findings should be interpreted with caution since the study did not compare dupilumab with standard treatments for different stages of COPD due to limited sample size. They go on to say that more studies are warranted to determine whether these results can be extrapolated to patients with COPD who do

not have the Type 2 comorbidities which prompted the treatment decision to prescribe dupilumab in the first place.

We note that this data is not directly applicable to the population of interest here, and therefore mortality must be modelled using other more appropriate data sources and methodologies. Nonetheless, these data are supportive of the expectation that reducing exacerbations and improving lung function does associate dupilumab treatment with decreased mortality.

3.2. Mortality risk due to exacerbations

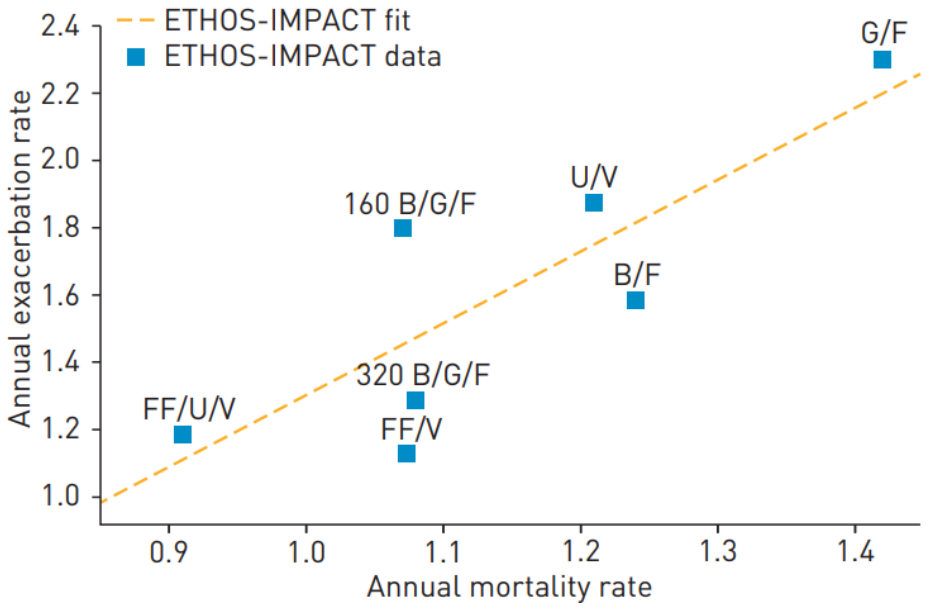
COPD patients carry a substantially increased risk of dying, compared to the age-matched general population. Progressive decrements to lung function and development of comorbidities increase risk (prominently cardio-vascular (Løkke 2023)), and exacerbation events then dramatically increase these risks acutely and for up to one year (Whittaker 2024).

Exacerbations, both moderate and severe, impact mortality directly and indirectly, and progressively.

1. Exacerbations and associated inflammatory processes cause damage to the lungs, resulting in a dramatic reduction in lung function. Even with appropriate medical intervention, patients are at clear and present danger of respiratory failure and death. Lung function recovers slowly, and some proportion is unrecoverable (permanent damage)
2. The risk of CV events increases dramatically during, and in the months following, an exacerbation, and these present known risks of death. The mechanisms for this increased risk are still to be elucidated, but impacts on CV function could be due to:
    a. Increased systemic inflammation “overflowing” to the CV system and causing damage (oxidative stress, atherosclerosis, endothelial dysfunction, arterial stiffness) (Morgan 2018)
    b. Physical hindrance to the functioning of the CV system from hyperinflated lungs (Balbirsingh 2022)
    c. Stress to the CV system from hypoxia and hypercapnia (Balbirsingh 2022)
3. Exacerbations increase the risk, severity and frequency of future exacerbations, compounding the above mortality risks progressively. (Suissa 2012)

Investigation of data from the IMPACT and ETHOS studies, in which ICS-containing therapies have proven to bring both exacerbation and mortality benefits, indicates a potentially linear and direct relationship between exacerbation and mortality rates (Andreas 2020). (Figure 3).

Figure 3. Exacerbation and mortality in the ETHOS and IMPACT trials (reproduced from Andreas 2020)



R^2 =0.70, p=0.018. B: budesonide; F: formeterol; FF: fluticasone furoate; G: glycopyrronium; U: umeclidinium; V: vilanterol

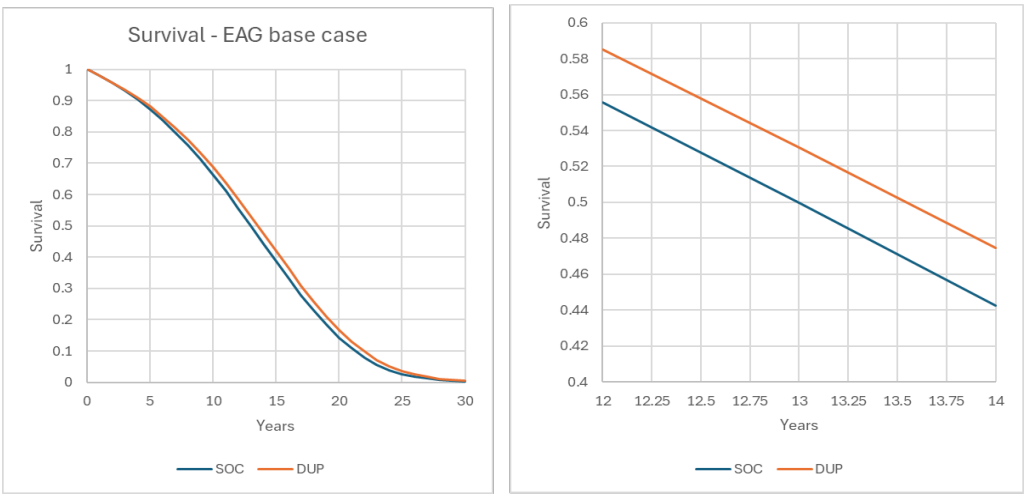
Such data is supportive of expert clinical opinion stating that ANY treatment that reduces exacerbations would be expected to consequently reduce mortality, such is the strength of the association. Given the strong link between exacerbations and mortality, and the dominant nature of this risk particularly with regard to CV risk, there is an imperative need for targeted treatment of COPD individuals at risk of exacerbations.

3.3 Correction to the presentation of the median survival estimates at committee and in the draft guidance.

3.3.1 Updated survival presentation

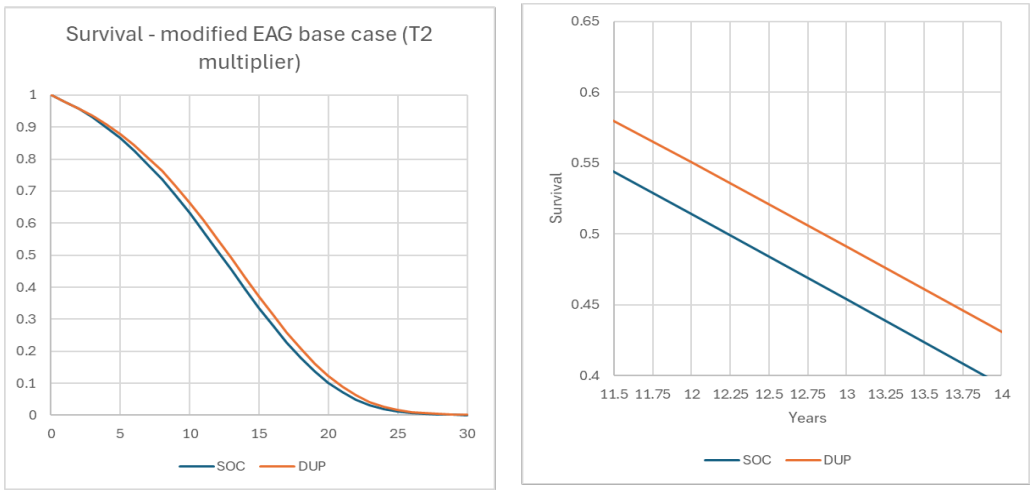
The survival plots presented at committee which informed the draft guidance (DG) mistakenly plotted year 0 as year 1. Inspection of those figures shows that at year 0 survival was less than 1. This incorrect plotting of the results is due to Markov trace in the economic model showing year 0 to denote the decision tree portion of the model before moving into the Markov at year 1. We have corrected this plotting error and updated the EAG base case estimate of median survival below in Figure 4. Median survival in the SoC arm of the model is ~13 years and for dupilumab it is ~13.5 years

Figure 4. Updated survival plots. EAG base case and detail showing duration at median survival.



Survival is plotted in Figure 5 for the committee preferred assumption of increased FEV1 decline due to Type 2 inflammation (hereafter termed the 'T2 modifier') including the other EAG adjustments. In this case median survival for SoC is ~12.25 years and for dupilumab it is ~12.75 years.

Figure 5. Updated survival plots. EAG base case with Type 2 multiplier and detail showing duration at median survival.



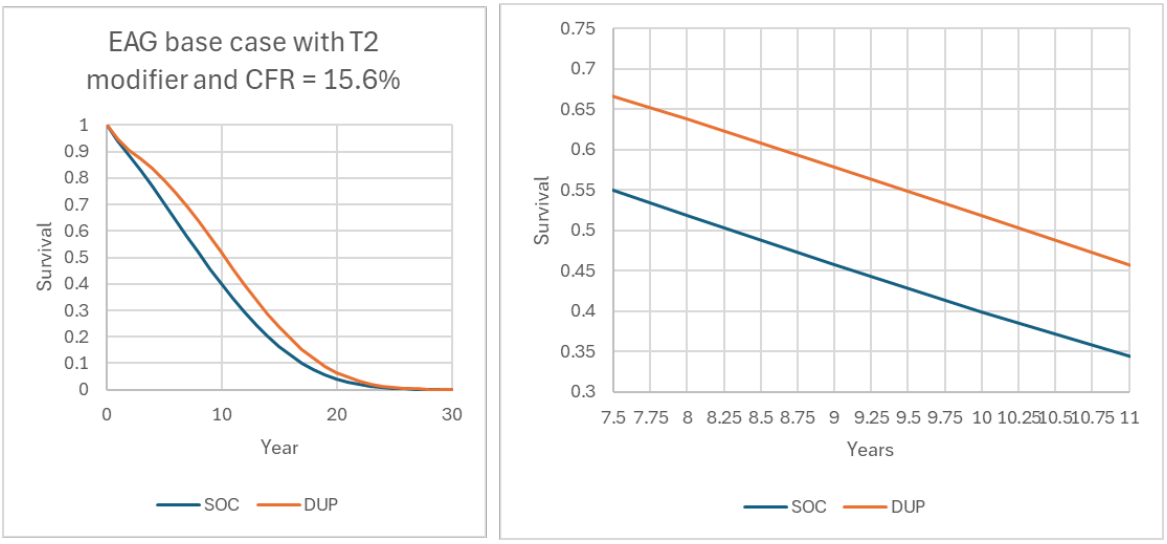
The updated representation of mortality above does not alter the ICERs.

All the survival analyses presented in this DG response below uses the correct expression of median survival.

3.3.2 Updated Sanofi base case

Survival for the updated Sanofi base case following the committee preference for the T2 modifier and inclusion of all other EAG base case adjustments apart from the removal of the CFR is presented in Figure 6.

Figure 6. Updated Sanofi Base case including EAG preferences but with T2 modifier and CFR = 15.6% and detail showing duration at median survival.



Median survival for SoC is ~8.25 years and for dupilumab it is ~10.25. (Note this is one year longer than stated in the DG due to the incorrect presentation of the survival curves.) The probabilistic ICER for the updated base case is £25,099 and deterministic ICER is £26,509. (Section 3.16 of the DG response).

3.4. Real world survival evidence in the population of interest.

3.4.1 Sources of evidence

There is a paucity of published evidence to describe survival outcomes for people with uncontrolled COPD and Type 2 inflammation, on current standard of care (triple therapy), which is the population of interest for this appraisal.

We have gathered further real world evidence matching as closely as possible the population of interest to validate the median survival predicted by the economic model. This evidence comes from three key sources developed by Sanofi and is supported by limited published literature. A summary of the real world sources is presented in Table 5 overleaf.

Table 5. Summary of the real world evidence for survival in the population of interest.

Source	Study description	Justification
English hospital episode statistics 2010 to 2019 (See Appendix A for more details of the study)	Observational retrospective longitudinal cohort study based on the inclusion and exclusion criteria for the BOREAS clinical trial taken from the liked hospital episodes statistics (HES), Clinical Practice Research Database (CPRD) Aurum, and Office for National Statistics (ONS). This study was primarily carried out to assess the rates of exacerbation in the real world in England to provide baseline rates for the economic modelling for the purposes of this appraisal. Limited mortality data was also collected. Study start was the January 1st 2010 and end was August 31st 2021.	The population in this study is considered relevant because the inclusion criteria were defined to align with the BOREAS dupilumab clinical trial population as closely as could be determined from health electronic records in England. Inclusion criteria are shown below (Exclusion criteria are provided in Appendix A): • Current or former smokers • 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. • Evidence of chronic bronchitis • Background triple therapy (ICS + LABA + LAMA) • Evidence of Type 2 inflammation: Patients with blood eosinophils ≥300 cells/microliter Three cohorts were collected. 1. The overall cohort meeting the above inclusion/exclusion criteria (n = 10,788) 2. The 'controlled cohort' defined as having no exacerbations in the past 12 months while on triple therapy. (n = 4,398) 3. The 'Uncontrolled' cohort defined as having Two or more moderate or one or more severe exacerbation within the past 12 months while on triple therapy. (**This is the population of interest for this appraisal**). (n = 3,747)
Burden of Chronic Obstructive Pulmonary Disease (COPD) uncontrolled under triple therapy in France – BREATH study (See Appendix B for more details of the study)	Observational retrospective longitudinal cohort study based on the Système National des Données de Santé (SNDS) database. The National Health Data System, SNDS covers ~99% of the French population. This study described the COPD burden according to treatment	This study was designed to collect mortality data in the French setting for a patient population with COPD uncontrolled on triple therapy and so is considered relevant. The COPD population in this study was collected according to the following inclusion criteria: • Patients aged ≥ 40 at index date. • Patients treated with triple therapy in 2015 (long-acting ß2-agonist (LABA), long-acting anticholinergic (LAMA) and inhaled corticosteroids (ICS)) for at least 90 continuous days prior to this event.

	lines, patients' pathways, costs and mortality associated with COPD in real-life in France. Patients treated for COPD with triple therapy in 2015 were included in the study. Five-year retrospective data were extracted.	This population (N = 186,963) was split into: 1. Population A1. The 'Uncontrolled' cohort. (**This is the population of interest for this appraisal**): Patients with at least one severe exacerbation or 2 moderate exacerbations in the 12 months preceding the index date. (n = 39,847) 2. Population A2: Patients from population A who were not included in population A1 (n = 147,116) A second population was collected for comparative purpose: 1. Sample randomly selected of 1 million individuals from the French population present in the SNDS in 2015 matching population A baseline characteristics. (n = 517,133)
Chronic obstructive pulmonary disease (COPD) mortality in the USA from the MarketScan database. (See Appendix C for more details of the study)	Retrospective observational cohort study to evaluate real-world mortality rates in patients with uncontrolled COPD and to describe patient characteristics, and treatment patterns in the United States using large claims databases (Merative MarketScan® and Medicare). The analysis was conducted on an extraction of MarketScan® data including COPD patients and randomly selected non-COPD patients matched on gender and age following the ratio 1:10 from year 2018 to 2022	This study was designed to collect mortality data in the US setting for a patient population with COPD uncontrolled on current treatment and so is considered relevant here. The COPD population in this study was collected according to the following inclusion criteria: • Patients were between 40-80 years old. • Patients were with ≥2 separate medical claims with an ICD-10 diagnosis code for COPD during the inclusion period (1st January 2018 and 31st December 2022), and the 2nd COPD claims occurred after the year 2019. • All selected patients were required to have one-year continuous enrolment in the pre-index (i.e., baseline) period. Three populations of interest were defined: 1. Case cohort: uncontrolled COPD population. Uncontrolled COPD patients were defined based on COPD exacerbation episodes throughout the entire study period among all the COPD patients. (**This is the population of interest for this appraisal**): (n = 54,710) 2. Control cohort 1: general COPD population (including uncontrolled COPD main population) (N = 226,996) 3. Control cohort 2: Non-COPD population (sample of general population without COPD diagnoses). (N = 415,849)

COPD = chronic obstructive pulmonary disease; EOS = eosinophil; FEV_1 = forced expiratory volume in 1 second; FVC = force vital capacity; LABA = long-acting β2-agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroids; HES = Hospital Episode Statistics, CPRD = Clinical Practice Research Database; ONS = Office for National Statistics; T2 = Type 2 immunity.

Key baseline characteristics for each study are presented side-by-side with the BOREAS and NOTUS pooled data in Table 6 below.

Table 6 Side-by-side comparison of age, sex and smoking status

Characteristic	Study			
	BOREAS/NOTUS pool	**HES database analysis**	**France – BREATH study**	**US - MarketScan database**
Age, years	65.1	69.97	68.88	Age range used for the analysis below is 65-74 yrs
Sex (male), %	66.8	56.02	60.76	45.08
Current smoker, %	29.8	50.39	N/A	N/A

3.4.2 England: Hospital episode statistics 2010 to 2019

Mortality data is limited from this study in the English population. (See Appendix A for more details of the study). However overall mortality was recorded for total deaths, exacerbation related deaths and non-exacerbation related deaths. The full dataset is presented in Table 7 below.

Table 7. Cause of death.

Cause of death	COPD Cohort* (n=10,778)		Controlled COPD (n=4398)		Uncontrolled COPD (n=3747)	
	n	**%**	**n**	**%**	**n**	**%**
Total deaths	4271	39.63	1706	38.79	1522	40.62
Exacerbation related	1431	13.28	503	11.44	601	16.04
CV related	870	8.07	344	7.82	302	8.06
Non-exacerbation and non-CV related	1966	18.24	856	19.46	618	16.49

*The definition for controlled COPD is no moderate of severe exacerbations in the previous 12 months whereas the uncontrolled cohort are patients with 2 or more moderate or 1 + Severe (with or without moderate) exacerbations. The overall cohort also contains patients with 1 moderate exacerbation. This explains why the controlled and uncontrolled cohorts do not sum to the overall cohort.

The total number of deaths recorded (all cause) in the uncontrolled COPD cohort of interest in the HES database study was 1522 across 3,747 patients. The total person-years of follow-up was 15,225.07. For the population of interest this represents a mortality rate of 99.97 per 1000 patient years. (84.44 per 1000 patient years for the controlled cohort and 89.32 per 1000 patient years for the total COPD cohort).

No time dependent all-cause mortality data is available from the study to allow a KM plot to be constructed. Assuming exponential decay, as only a single rate is available, the median can be calculated as ln(2)/R. In this case R is 9.997% and so the median for this population can be estimated at 6.93 years. The SE around the estimate can be estimated from the number of deaths (1522) and number of patients-years (15,225.07). SE = sqrt(1,522)/15225.07 = 0.0026. The Lower 95% CI = mortality rate - 1.96*SE = 0.09494, leading to a median survival of 7.3 and the upper is + 1.96*SE = 0.10499 leading to a median survival of 6.6 years.

Limitations

Whilst this 'uncontrolled' population taken from the HES database derived from the BOREAS inclusion criteria is likely to be most closely related to the population of interest, limited mortality data is available from the study (for e.g. time dependent data is not available). However, the

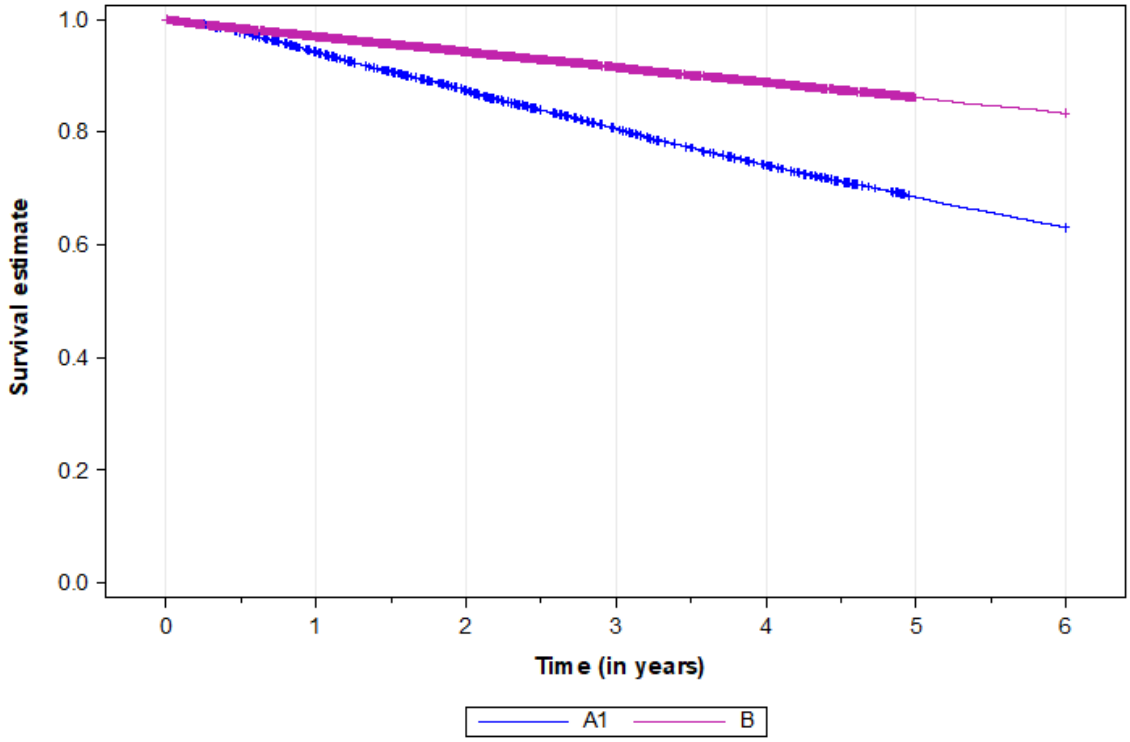
available data does allow calculation of mortality rate per 1000 patient years (99.97 / 1000 patient years) from which we have estimated a median survival of **6.9 years** (95%CI: 6.6 to 7.3 years)

3.3.3. France – BREATH study

Substantial mortality data including time dependency is available in this study, compared to the English based HES database study. (See Appendix B for more details of the study). For population A1 (the population of interest, see Figure 7), there was a total of 35,870 individuals, among whom 13,159 events were observed. The median survival time was not reached, indicating that more than half of the individuals were still alive at the end of the study. The Kaplan Meier plot for mortality is shown in Figure 7.

To derive estimates for median mortality the 'A1' KM plot was fitted to several parametric estimators. The plots for these are shown in Figure 8 and the fit statistics along with estimated median mortality in each case are provided in Table 8 and Figure 9.

Figure 7. Kaplan Meier modelling of survival in the uncontrolled cohort (A1) and the general population cohort (B)



At risk							
A1	35,870	33,711	31,238	28,714	26,357	24,275	22,368
B	71,740	68,368	65,991	63,408	61,120	58,889	56,957
Cumulative events							
A1	0	2,101	4,492	6,922	9,242	11,252	13,159
B	0	2,138	4,031	5,943	7,798	9,657	11,589
Survival							
A1	1.00	0.94	0.87	0.81	0.74	0.68	0.63
B	1.00	0.97	0.94	0.92	0.89	0.86	0.83

Figure 8. Parametric fits for the KM curve A1 from the French BREATHE study.

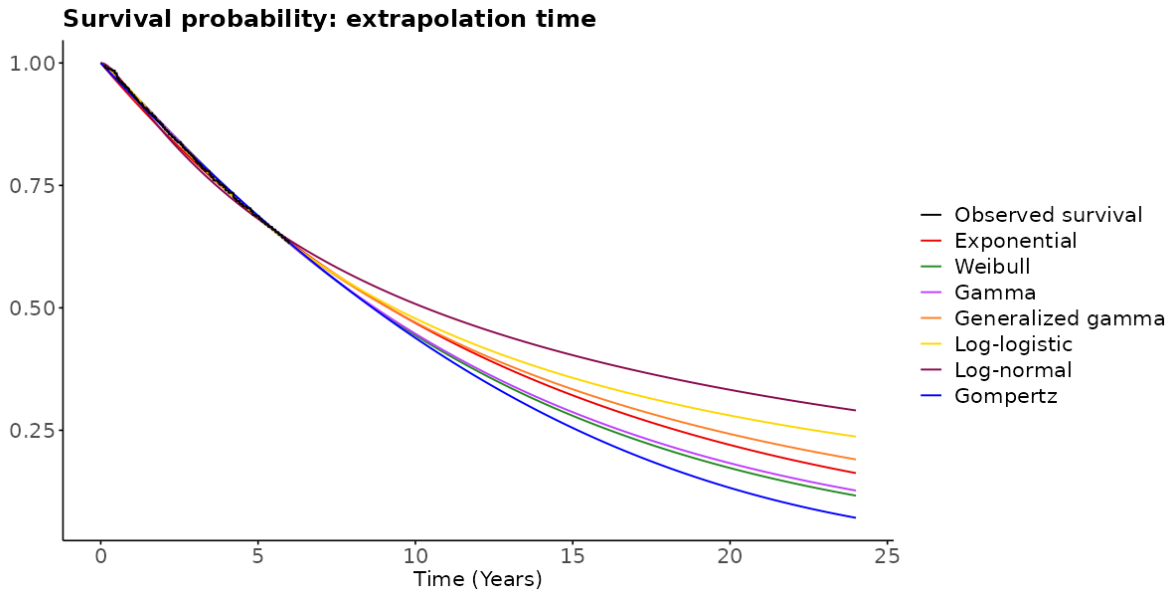
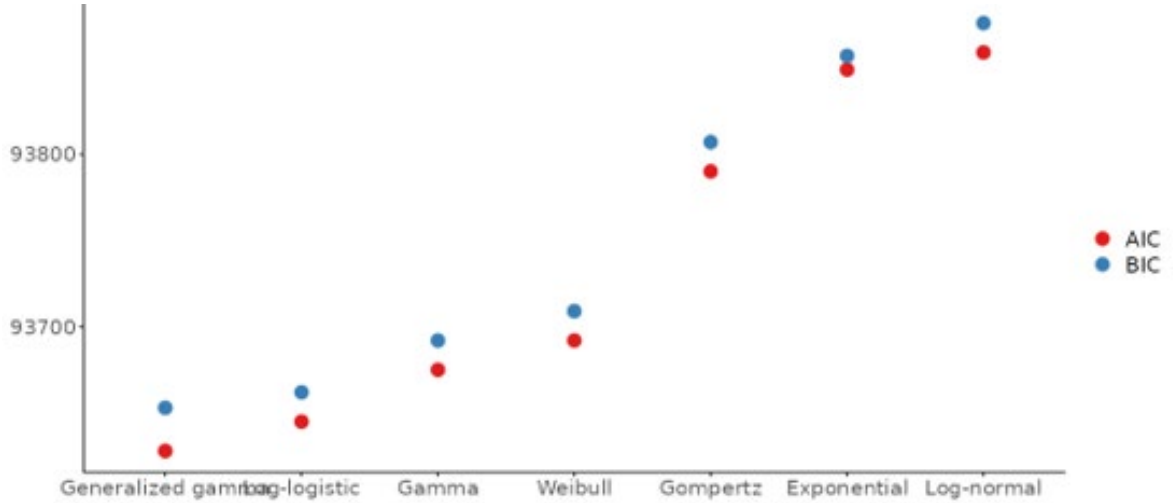


Table 8. Goodness-of-fit statistics for the fitted distributions and estimated median mortality

Distribution	Parameter estimate	Underlying hazard	AIC	BIC	Estimated median mortality
Exponential	Rate = 0.0757	Constant	93849	93858	9.16 (9.00, 9.32)
Weibull	Shape = 1.118, Scale = 12.0607	Increasing	93693	93710	8.67 (8.52, 8.84)
Gompertz	Shape = 0.0374, Rate = 0.0680	Increasing	93791	93808	8.64 (8.46, 8.81)
Log-logistic	Shape = 1.2345, Scale = 9.3186	Increasing then decreasing	93646	93663	9.32 (9.14, 9.52)
Log-normal	Meanlog = 2.333, sdlog = 1.5312		93859	93876	10.31 (10.08,
Gamma	Shape = 1.1483, Rate = 0.0961	Increasing	93676	93693	8.72 (8.58, 8.87)
Generalised gamma	Shape = 0.6073, Scale = 2.5438, Location = 1.1402	Decreasing	93628	93654	9.15 (8.95, 9.36)

AIC = Akaike information criteria; BIC = Bayesian information criteria

Figure 9. Model performance



Inspection of Table and Figure indicates that the generalised Gamma model is the best fit to the data. Median mortality using this distribution is 9.15 (95% CI: 8.95, 9.36) years. However, the underlying hazard function in the generalised gamma in this case is decreasing as the shape parameter is <1 (0.603). This makes the generalised gamma less likely to be a credible model. Similarly, the log logistic and log normal functions are less applicable as these function feature longer term decrease in hazard function after an initial increase. The exponential function which has an underlying constant hazard provides an estimate of 9.16 years for median survival. The remaining three functions with increasing hazard provide a tight range for the estimate from 8.64 (Gompertz) through 8.67 (Weibull) to 8.72 years (Gamma). Using the best fit for these estimators (Gamma) the most plausible median survival in this population is 8.72 years.

Limitations

Whilst these data represent the most complete dataset we have from which to calculate median mortality, it is likely that it will be overestimated for the English setting in the population of interest for the following reasons.

- These data are collected in the French setting where it is known that mortality outcomes for patients with COPD are generally better than in the UK (Mei 2022).
- Whilst cohort A1 matches as closely as possible the population of interest, the average age of patients in the study was just over 1 year younger than the population represented in the HES database study above.
- Eosinophil (EOS) count is not available in the database and so the population may not be at as high risk of exacerbation and mortality as the Type 2 patient with ≥300 blood eosinophils/µL.

3.3.4. US – MarketScan database

Mortality data is only available at years 1, 2 and 3 in this study stratified according to age. (See Appendix C for more details of the study). Table 9 shows the raw all-cause mortality during three-year follow-up after the index date for the uncontrolled COPD population aged 55 and above.

Table 9. Raw all-cause mortality during three-year follow-up after the index date

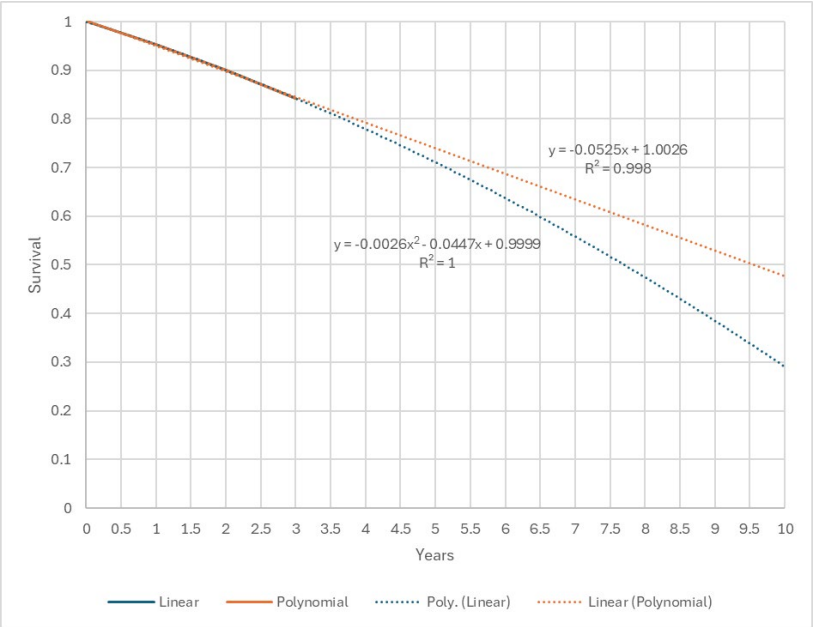
Age at start of observation period	N at start of observation period	Year 1		Year 2		Year 3	
		Cumulative mortality events	Cumulative survival	Cumulative mortality events	Cumulative survival	Cumulative mortality events	Cumulative survival
55-64 years	21,001	250	0.9881	503	0.976	777	0.963
65-74 years	15,125	706	0.9524	1,508	0.9003	2,386	0.8422
75+ years	8,111	558	0.9312	1,227	0.847	1,896	0.7662

The patient characteristics at baseline for the English and French real world data shown in Table , suggest that the average age of patients in the population of interest is around 69 to 70 years old. Therefore, the most appropriate data to include in an extrapolation from the US market scan dataset to generate estimates for median survival in an equivalent English population is the dataset for patients aged 65 to 74.

The cumulative survival for this cohort is plotted in Figure 10. Only 3 points are available in the dataset and so very simple linear and polynomial fits generated in excel have been used to establish a plausible range for survival. The extrapolations are presented in Figure 10. Median survival in the

population of interest might be expected to be around 8.5 years (mid-point of the range) with a range of 7.5 to 9.5 years.

Figure 10. Cumulative survival for the cohort aged 65 to 74 from the US MarketScan database



Limitations

Whilst we have picked the age range from the study to be most representative of the population of interest (65-74 years), this dataset is limited to annual datapoints for three years, by which time only 15% of patients have died. This makes extrapolation of the data to generate median survival uncertain. We have provided two options a linear and a best fitting polynomial. (It should be noted that the polynomial fit (y = -0.0026x^2-0.0447x+0.9999) has a very slightly decreasing hazard: Negative coefficient for the slope in the first derivative: dy/dx=−0.0052x−0.0447). This provides an indicative range using a simplistic approach to extrapolation and we have taken the midpoint at 8.5 years as the point estimate. Nonetheless this estimate is in accordance with the French BREATHE study above. Again, this may be an overestimate for the English population for the following reasons.

- The study is US based and so may not be generalisable to the UK
- Linkage between claims data and laboratory data resulted in the collection of eosinophil levels for only 1% of the patients of the extraction and so the population represented in this study is not exclusively Type 2.

3.4. Published literature

3.4.1 Rothnie 2018. Natural History of Chronic Obstructive Pulmonary Disease Exacerbations in a General Practice–based Population with Chronic Obstructive Pulmonary Disease

There is very little literature precedent to establish median mortality in the population of interest for English patients. An alternative to the approaches taken above is to estimate mortality based on prior exacerbation history, analogous to the ‘uncontrolled’ criteria for the population of interest.

One study carried out relatively recently provides mortality estimates following exacerbations in the English setting. [Rothnie, 2018]. This was a retrospective case-control cohort study on 99,574

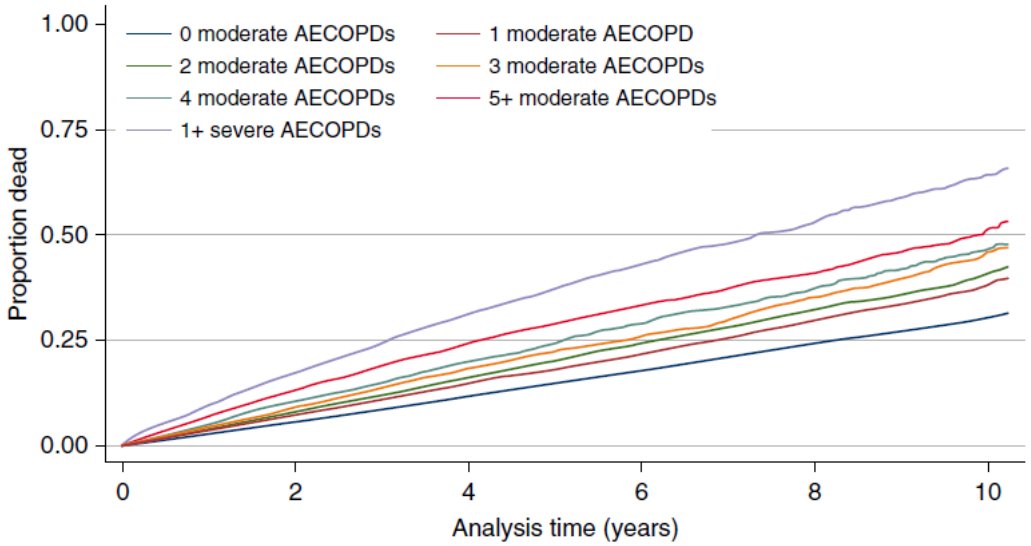
patients with COPD from 2004 to 2015, taken from the UK Clinical Practice Research Datalink (CPRD). Patients were included in the study according to the following criteria:

1. Patients aged older than 35.
2. Patients with included in the CPRD with a validated diagnostic code for COPD.
3. Patients with a smoking history.
4. Patients eligible for linkage with:
    - Hospital Episodes Statistics
    - Office of National Statistics
    - Deprivation data (index of multiple deprivation)
5. Patients with at least 1 year between joining the database and censoring at death or moving outside the system.

The exposure categories were, one, two, three, four or five or more moderate exacerbations and no severe exacerbations, and one or more severe AECOPDs (and any number of moderate exacerbations). Patients were categorized into these groups during their first year of available data post-COPD diagnosis, referred to as the "baseline period." Outcomes were then tracked during the follow-up period, starting from the end of the baseline period, for up to a maximum of 10 years.

Survival in each of the baseline exacerbation categories is shown below (Figure 11 taken from Rothnie 2018).

Figure 11. Time to death by baseline exacerbation frequency and severity.



In the category with one prior severe exacerbation in the previous year median survival is ~7.5 years with longer survival for the population with moderate exacerbations. Survival in a population consisting of both people with and without severe events at baseline which is the population of interest may therefore be longer than 7.5 years. For example, in the 5+ moderate category survival is 10 years. Nonetheless, this provides a median survival estimate in line with the other sources of evidence above.

Limitations

Patients were categorized into the exposure categories during their first year of available data post-COPD diagnosis. This was the “baseline period.” Outcomes were then ascertained during follow-up

period starting from the end of the baseline period, up to a maximum available follow-up of 10 years and 2 months. Patients were required to have survived at least 1 year during follow-up.

We interpret this to mean that patients who died within 1 year of the index event would not have been included in the database. It is clear from the NACAP data that there is at least a 12 % risk of mortality in the 90 days post exacerbation, and we have used the more credible estimate of 15.6% in our modelling. Hence the population at risk in Rothnie may not include the most vulnerable patients and the overall estimate of survival above 7.5 years could be slightly too long.

3.4.2. Suissa 2012: Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality

A long-term Canadian study (17 years of follow-up to March 2007) was mentioned at committee as a potential source for median mortality. [Suissa 2012]

Patients were included in the study between 1990 and 2005 if:

- They were dispensed at least one prescription for respiratory medications including ß agonists, theophylline, ipratropium bromide, tiotropium, inhaled corticosteroid, nedocromil, ketotifen, cromolyn or anti-leukotriene.
- Had a hospitalisation with a primary discharge diagnosis of COPD (International Classification of Diseases ninth revision (ICD-9) codes 490e492 and 496, ICD-10 codes J40eJ44).

Subjects were excluded if:

- They were aged <55 years at the time of this first hospitalisation
- Had a prior asthma hospitalisation

The study included 73,106 hospitalised patients, of whom 50,580 died during the 17-year follow-up period (mean follow-up=3.6 years), with 50% and 75% mortality at 3.6 and 7.7 years respectively.

In this study median survival was very low (3.6 years), however, the population included does not match the population of interest for this appraisal. Inspection of the patient characteristics at cohort entry show that the patients had a mean age of 75.4 (+/- 8.4) years. This is around 10 years older than the pooled population from BOREAS and NOTUS and 5.5 years older than the population identified in the English HES study described above.

The study found that the rate of death increased by 66% with each additional decade of age (HR 1.66; 95% CI: 1.64, 1.68). This supports the conclusion that this older age group will have considerably lower median survival than for the younger population of interest in this appraisal. Furthermore, by definition, patients must have experienced a hospitalised event implying higher mortality risk for the entire cohort, which is not the case in the BOREAS/NOTUS population. These data are less applicable to the decision problem than the other evidence presented above.

3.5. Discussion

We have made best efforts to estimate median mortality in the population of interest using available data from large datasets. The estimated range is from around 4 to 9 years with the most credible estimates falling within the range 6.9 to 8.7 Table 10.

Table 10. Median modelled survival from the real world evidence

Source	N	Current SoC estimated median survival (years)*	
		Point estimate (years)	Plausible range (years)
Company base case model*	-	8.3	N/A
English HES data	3,747	6.9	6.6 to 7.3
French BREATHE study**	35,870	8.7**	8.6 to 9.15
US MarketScan	15,125	8.5***	7.5 to 9.5
Rothnie 2018***	99,574	7.5	Up to 10
Suissa 2012	73,106	3.6	N/A

* Survival for the updated Sanofi base case following the committee preference for the T2 modifier and inclusion of all other EAG base case preferences apart from the removal of the CFR (CFR used = 15.6%)
** Using the best fit for the estimators with increasing hazard (Gamma)
*** Center of the range between linear and polynomial fits

The limitations to each estimate have been discussed above and are summarised below.

The Canadian Suissa 2012 data suggesting median survival of <4 years is too short because it is in a population much older than might be expected in the English setting for patients eligible for dupilumab. However, age is not the only consideration. The eligibility criteria for the Suissa study specified a severe hospitalised exacerbation which is known to be a strong predictor of future mortality. The dupilumab eligible population is uncontrolled patients with Type 2 inflammation. Uncontrolled disease is characterised as ≥2 moderate OR ≥1 severe historical exacerbations within 12 months, hence it is not a requirement that there is severe exacerbation history. This means that longer survival overall is expected in the dupilumab eligible cohort in current clinical practice, making the Suissa data less applicable to the decision problem.

The medians calculated from French, US and Rothnie studies at around 7.5 to 8.5 years may overestimate survival as these populations are not Type 2, and in the French case outcomes are known to be more favourable than in England. (Age standardised mortality / 100,000. France: 8.9 (7.7 to 9.7). UK: 26.2 (23.4 to 27.6) taken from International Respiratory coalition [ERS 2025]). The estimate taken from the English HES data at ~6.9 years provides a lower bound.

The slightly longer median duration derived from the trial population is predictable as clinical trials are typically conducted in younger, fitter patients than might be expected to receive the medicine in real world clinical practice.

We validated these estimates with several clinicians during 1:2:1 conversations during the DG consultation period and the consensus was that in the population of interest a median survival of 7 to 8 years could be credible, but may be slightly conservative as the HES database study suggests slightly shorter median survival (6.9 years).

The updated Sanofi base case after ACM1, including the Hoogendorn CFR of 15.6%, Whittaker 2024 SMR and the T2 modifier (along with all other EAG preferences), provides credible survival median survival estimates for the population of interest, in line with multiple real-world evidence sources. As such, the company's base case is credible and appropriate, and is fit for decision making purposes. Exploration of the ICERs derived from the updated model are presented in Section 9 below.

4 Data estimating how much of the mortality in the population covered by the evaluation is attributable to exacerbations (Section 3.11 in the Draft Guidance)

In this section we further validate the assumptions underpinning the mortality modelling in the economic evaluation using the real-world evidence analysis from linked HES-CPRD data described above in section 3.4.2 and in Appendix A. The study population is highly relevant as it included COPD patients in England between 2010 to 2021 who had raised EOS ≥300 cells/µL, on triple therapy and had ≥2 moderate or ≥1 severe exacerbation in the previous year. This is the population of interest.

The relevant data is provided in Table 7 above. In the population of interest (n = 3,747), 1,522 patients died, including 601 exacerbation-related deaths, 302 CV-related deaths and 618 deaths due to other causes. This corresponds to 39.5% of total deaths related to exacerbations during the study period.

In the economic model using the Sanofi base case settings (See section 9 describing the updated model) the contribution of exacerbations to mortality is 41%. This aligns with the real world evidence.

5 Further evidence to support applying a CFR to account for the increased risk of mortality from exacerbations in addition to the SMRs to estimate mortality associated with COPD severity (Section 3.11 in the Draft Guidance)

In this section we discuss literature precedent for the approach taken in our model (Section 5.1) and discuss the rationale for the use of both a CFR and an SMR in the modelling (Section 5.2).

5.1. Literature modelling precedent

Recent health economic models in COPD, including those developed in the United States and Canada, have independently applied both a case fatality rate (CFR) for exacerbations and standardised mortality ratios (SMRs) for disease severity to estimate overall mortality.

Across the four most recently published models, this dual approach has been consistently used to reflect the increased short-term risk of death associated with severe exacerbations to recognise the well-established link between exacerbations and mortality, alongside the underlying long-term mortality risk according to lung function severity (SMRs are applied for each FEV1-related health state).

It is critically important to include the CFR as the model must account for both the increased risk of mortality with exacerbations *and* the impact of mortality due to the differential in exacerbation rates between arms. This can't be achieved by only using the same SMR in each arm per health state. The most recently published models are presented in Table 11 below.

Table 11 Recent health economic models in COPD applying both a case fatality rate (CFR) for exacerbations and standardised mortality ratios (SMRs)

Source	Setting	Comparison	Source of SMR	Source of CFR
Johnston 2024.	Canada	Dual vs triple inhaled therapy	Shavelle 2009	8.81% based on an audit of COPD hospitalization data in Ontario.
Trigueros 2022	Spain	Dual vs triple inhaled therapy	Shavelle 2009	12% estimated mortality 90 days after hospitalization for a

				severe exacerbation. UK NACAP (National COPD Audit Programme)
ICER 2024	United states	Ensifentrine vs SoC (triple or double therapy)	(Atsuo 2011)	15.6% Hoogendorn 2011
Leerink Center for Pharmacoeconomics 2025	United states	Dupilumab vs SoC (triple therapy)	(Atsuo 2011)	15.6% Hoogendorn 2011

Collectively, these evaluations support the use of SMRs, and exacerbation-related mortality estimates as a clinically valid and methodologically sound means of capturing long-term disease burden and treatment benefit. This consistency strengthens the external validity of the present analysis and ensures alignment with prevailing standards in health economic modelling of COPD.

5.2. Use of CFR and SMR in the Sanofi modelling following literature precedent

It is imperative that the economic modelling of mortality in the assessed COPD population captures fully the risks associated with individual exacerbation events to model survival accurately, and that the differential ability of dupilumab versus SoC to reduce exacerbations is accounted for. Therefore, the economic model features a case fatality rate (CFR) for every severe exacerbation event modelled in the population.

As a key driver of mortality some models have featured only a CFR, notably in TA461 (Roflumilast) where NICE accepted 15.3% as the value to be used for morality associated with severe exacerbations. Note that moderate exacerbations also carry a significant risk or mortality, albeit at a lesser rate than severe exacerbations, and that therefore such a CFR conservatively estimates the impact of exacerbations on mortality (and the impact of exacerbation reduction with dupilumab versus SoC).

The most appropriate source of data for estimating a severe exacerbation case fatality rate is the Hoogendorn study. This is because a severe exacerbation increases risk of death from respiratory failure and CVD that peaks early but then has an extended “tail” of effect. It is known that some additional risk of mortality can last for at least one year. Hoogendorn does not arbitrarily assign a period for increased risk (such as 30 days or 90 days as in NACAP) but instead calculates the full risk over time, over and above the background risk of mortality for COPD. We have provided further justification for the use of the Hoogendorn estimate in Section 6.2 below.

Recognising that some of the mortality risk for COPD is not related to exacerbations, more recent modelling methodologies add a Standardised Mortality Rate (SMR) to the CFR. (See section 5.1 above).

Therefore, in our model we have included SMRs from the most recently published English data (Whittaker 2024), broken down by GOLD severity to align with the health states in the model. This captures additional non-exacerbation-related mortality.

The committee have concerns regarding possible double counting of severe exacerbation risk using these two data sources since the authors of Whittaker 2024 state that exacerbations are controlled for at baseline. We remain unconvinced that there is double counting for the following reasons

- The HR for GOLD severity describes the relative change in mortality based on GOLD severity stage, while keeping previous exacerbation rate constant, and is therefore independent of

the frequency (or occurrence) of previous exacerbations. i.e. the HR for GOLD severity is not affected by differences in the occurrence of previous exacerbations because these effects have already been accounted for in the Cox model adjustment.

- Recent exacerbations are predictive of future exacerbations, so the risk changes over time, and it is therefore relevant to include the influence of exacerbations prospectively in the Markov model with a CFR.

However, recognising that some doubt regarding the influence of severe exacerbation-related mortality on the SMR remains, we are confident that any such component is unlikely to be substantively captured (and therefore double counted) within the model, utilising the Hoogendorn CFR and Whittaker 2024 SMR.

Whittaker is the best available published data to inform SMRs, but we recognise these rates are derived from the general COPD population with no differentiation by EOS level and with an expected lower risk of exacerbations and mortality, compared to the population of interest. Of the Whittaker 2024 population at baseline:

- Approximately two thirds are expected to not have evidence of Type 2 inflammation
- Of those patients with FEV1 measurement, nearly 80% (78.7%) were in the mild or moderate COPD categories.
- Over two thirds had no prior exacerbations
- We have calculated that only 4.3% of patients had 1 or more severe exacerbations, corresponding to a severe AER of approximately a very low 0.02 (See Appendix E for details)

Therefore, the capture of mortality specifically due to severe exacerbations in the Whitaker 2024 SMR is expected to be very low, predicting minimal risk in 'double counting' the mortality due to severe exacerbations, when adding this SMR to the CFR.

Mortality risk from exacerbations using a CFR in the model is only attributable to severe events. At baseline in Whittaker 2024 only 4.3% of patients had 1 or more severe exacerbation. This contrasts with the real world evidence from our HES study which shows that at baseline (in the year prior to study start) 26.2% of patients experienced a severe exacerbation. (See Table 1 and following text in Appendix A). There is literature precedent to indicate that moderate exacerbations also carry a risk or mortality, albeit at a lesser rate than that for severe exacerbations. The unadjusted mortality rate per 1000 patient years in Whittaker 2024 is 47.5 (47.1 to 47.9) for patients with no prior exacerbations and the rate for the smaller group of patients with any (moderate or severe) prior exacerbations was 64.2 (63.5 to 64.9). The weighted average rate between these groups (ALL patients) is 52.4 / 1000 patient years. (See Appendix D for calculation). This shows the small influence on mortality that may be due to exacerbations in the overall patient population (an extra ~4.9 / 1000 patient years or 0.49%). The HES database study above has provided an estimate for mortality of 99.97 / 1000 patient years which is considerably higher reflecting the likely influence of mortality due to exacerbations in this higher risk population. We have provided a scenario where the CFR is inflated to account for moderate exacerbations in the relevant patient population in the absence of an SMR in Section 7.2 below. This analysis provides estimates for median survival which are in line with the real world mortality, discussed above in Section 3).

The most effective way of validating our methodology (beyond analogy to literature precedent. See section 5.1 above) is to assess the overall expected median survival for this specific population according to the economic model, against other sources of data and expert clinical opinion. Survival has been discussed above in Section 3 and alternative sources or the CFR are provided in Section 6

below. Comparison of the various scenarios shows that the Hoogendorn severe exacerbation CFR and the Whittaker SMRs together do accurately model mortality for the BOREAS & NOTUS population with an estimate of median survival at 8.3 years using the best available data.

6 Sources of evidence for the CFR (Section 3.11 in the Draft Guidance)

In this section we discuss alternative CFR rates and their impact on the outcomes in the model using the updated Sanofi base case following ACM1. This is followed by further justification for the use of our chosen value of 15.5% [Hoogendorn 2011] We discuss the impact of modelling different rates on median survival in Section 6.3 below.

We have provided a **range of alternatives for the CFR** but all of these with the exaction of Wildman 20026 **increase median survival in the model**.

The Hoogendorn study provides the most robust estimate for the CFR, capturing both acute and long-term mortality risk without relying on arbitrary timeframes like 30- or 90-day cutoffs. Unlike traditional sources such as NACAP, which report all-cause mortality (e.g., 12% over 90 days), Hoogendorn isolates the excess mortality directly attributable to the exacerbation by comparing observed survival with a modelled baseline, avoiding double counting and enabling accurate pairing with standardised mortality ratios (SMRs). The study found a weighted mean CFR of 15.6% (95% CI: 10.9%–20.3%), consistent with accepted benchmarks and supporting credible long-term survival estimates. While the EAG noted the data is older and non-UK based, treatment practices have changed little, and UK mortality remains higher than most of Europe—suggesting Hoogendorn may even underestimate UK risk. Therefore, it remains the most appropriate and comprehensive source for modelling severe exacerbation CFR in COPD.

We have also explored the impact of changing the CFR by 5% increments and shown that **CFR = 40% would be needed to reach median survival as low as 5 years** with a consequent reduction in the probabilistic ICER of ~£6.5k).

6.1. List of alternative CFR rates

Table 12. Alternative sources for the CFR.

Source	Parameter estimate	SOC Median modelled survival duration (years)	Justifications
		65 years	
EAG base case	0%	12.5	It is not reasonable to ignore the impact of exacerbations on mortality. This is because there is no mortality differential between the arms and this methodology produces overlong median survival duration.
Hoogendorn 2011	15.6%	8.25	Sanofi Base case – see section 6.2 below.

<table>
<tr><td>NACAP (30 day survival)</td><td>6.1%</td><td>10.4</td><td rowspan="2">These data are not appropriate for use in the model.
The national clinical audit data is from 107,761 adults with COPD admitted to UK hospitals with a COPD exacerbation between 2018 and 2020. Of these patients 6.1% died within 30 days of admission and 11.9% died within 90 days of admission.
These data use arbitrary cut offs at 30 and 90 days for policy and reimbursement reasons. It is not reasonable to expect that mortality will be bound by these constraints. For example, lung function reduces post exacerbation and never gets back to where it was.
Published data supports that mortality impact of a hospitalised exacerbation can be much longer than 90 days (See Wildman 2009 below) and so the CFR can reasonably be expected to be above 12%. This extended period of elevated risk not captured in the 90 day arbitrary cut off.</td></tr>
<tr><td>NACAP (90 day survival)</td><td>11.9%</td><td>9.0</td></tr>
<tr><td>Whittaker 22</td><td>Applied as an incident Rate Ratio<table><tr><td></td><td>Excess mortality, IRR</td></tr><tr><td>Exacerbation type</td><td>Relative to no exacerbations</td></tr><tr><td>1 Moderate exacerbation</td><td>1.08 (1.04- 1.12)</td></tr><tr><td>2 Moderate exacerbation</td><td>1.16 (1.10 – 1.22)</td></tr><tr><td>3+ Moderate exacerbation</td><td>1.32 (1.26 – 1.39)</td></tr><tr><td>1 Severe exacerbation</td><td>1.75 (1.66 – 1.85)</td></tr><tr><td>2 Severe exacerbation</td><td>2.33 (2.10 – 2.58)</td></tr><tr><td>3+ Severe exacerbation</td><td>2.87 (2.53 – 3.25)</td></tr></table></td><td>10.4</td><td>These data do incorporate mortality risk due to moderate exacerbations but when applied to the low underlying risk (SMRs from Whittaker 24) do not appropriately model survival duration.
Excess mortality applied as an Incident Rate Ratio (IRR) is relative to patients who experience no recent exacerbations. The SMR sources to which these would be applied is Whittaker 22, which are taken from the general COPD population (NOT spilt into high/low eos cohorts) which is not the high-risk population we are considering in this appraisal.
Because the IRR is a relative rate applied to an underlying SMR that is likely to overestimate survival these IRRs are less applicable to the patient of interest here who is the T2 exacerbating patient uncontrolled on current treatment at higher risk of exacerbation and death.
Using the IRRs from Whittaker results in over long median equivalent to the NACAP 6.1% estimate at 10.4 years whereas using the CFR which directly accounts for the exacerbation event itself, not relative to an underlying overestimate of survival</td></tr>
<tr><td>Roflumilast, TA461 Connolly 2006</td><td>15.3%</td><td>8.3</td><td>Committee preferred assumption in TA461. More consistent with the estimate from Hoogendorn 2011. Note that TA461 did not include SMRs.</td></tr>
<tr><td>Wildman 2009</td><td>37.9%</td><td>5.5</td><td>180 day mortality associated with a hospitalised COPD exacerbation including ICU stay. This is a higher estimate in more severe exacerbating patients. However, this does indicate that the influence of a severe hospitalised event is likely to extend beyond 90 days.</td></tr>
</table>

6.2. *Justification for use of Hoogendoorn 15.6% CFR*

The most appropriate source of data for estimating a severe exacerbation case fatality rate is the Hoogendorn study. A severe exacerbation elevates risk of death from respiratory failure and CVD that peaks early during the hospital stay, but then has an extended "tail" of effect post-discharge, extending for over one year.

Traditional approaches to estimating CFR, such as the 30-day or 90-day mortality values commonly used in sources like the NACAP data (which reports 12% mortality over 90 days post-severe exacerbation), rely on arbitrary time cutoffs, typically useful for policy and reimbursement decisions rather than clinical or epidemiological accuracy. Additionally, these approaches capture all-cause mortality over the time period, not just the increased risk due to the exacerbation. Hoogendorn takes the approach of not arbitrarily assigning a period for increased risk and instead calculates the full extended risk over time, over and above the background risk of mortality for COPD in the following way:

- Avoids arbitrary time cutoffs and instead models the true excess mortality attributable to the exacerbation.
- Fits a survival curve to the stable post-hospitalisation phase and extrapolates it back to admission, allowing for a comparison with the actual observed survival curves
- Calculates excess mortality as the area between these two curves, representing the total mortality burden associated with the exacerbation.

This method captures both the acute and long-term mortality impacts of hospitalised exacerbations, leading to a more comprehensive and credible CFR estimate. And the CFR itself excludes background mortality due to other causes over this period, allowing appropriate partnering to an SMR which captures background mortality throughout the model lifetime. (Note that using the NACAP data at 90 days would double count mortality as this accounts for all-cause mortality across 90 days).

Across the individual studies included in the Hoogendorn meta-analysis, CFR estimates ranged from 11.4% to 19.0%, with no discernible decline over the 10-year study period. The overall weighted mean CFR was 15.6% (95% CI: 10.9%–20.3%). This figure not only aligns with accepted benchmarks (e.g., TA461 accepted 15.3% from Connolly et al. for roflumilast) but also supports credible long-term survival estimates in the model (7 to 8 years), adding further validity for use in this assessment.

The EAG have commented that Hoogendorn is based on relatively older data (before 2005) and from non-UK COPD patients. However, we believe this estimate is still valid for the following reasons:

- The acute treatment of severe exacerbations has not changed considerably during the last 20 years; the use of non-invasive ventilation has increased, but the impact of this on mortality is controversial. Overall, this is consistent with COPD mortality year on year since 2005, and 2014 UK Audit and 2023 NACAP data both estimating 90-day severe exacerbation mortality risk at 12%, indicating that the older data is still valid.
- Mortality figures for COPD in England are considerably worse than those for almost all other European countries. Therefore, Hoogendorn data based primarily on non-UK EU data, may be an underestimate of UK severe exacerbation mortality risk.

Overall, Hoogendorn is the best available data to inform the severe exacerbation CFR in the model.

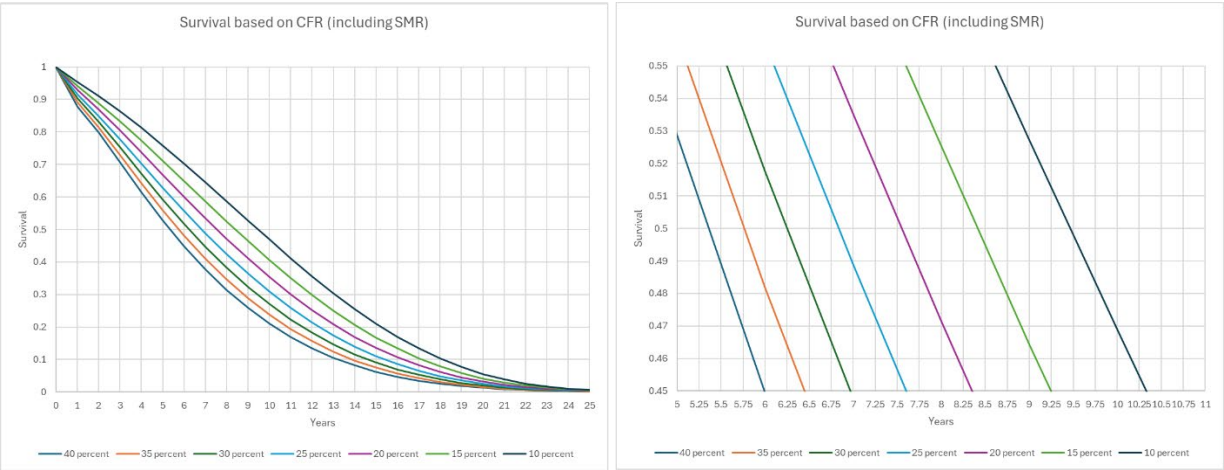
6.3. *Exploration of CFR on modelled mortality and impact on the ICER*

To visualise the impact of different rates for the CFR we have modelled curves for the SoC arm from BOREAS/NOTUS pooled population and derived the ICERs. For these estimates we have used the Sanofi base case model which has a starting age of 65 as observed in the studies. In Figure 12 we show the impact of a 5% increase in the CFR from 10% to 40% on top of SMR and the corresponding ICERs are provided in Table 13

Table 13 ICERS at different CFRs between 10% and 40% with background mortality (SMR) included.

CFR (%)	Median survival (years)	With underlying SMR	
		Probabilistic ICER	Deterministic ICER
10	9.4	[redacted]	[redacted]
15	8.4	[redacted]	[redacted]
20	7.6	[redacted]	[redacted]
25	6.8	[redacted]	[redacted]
30	6.2	[redacted]	[redacted]
35	5.8	[redacted]	[redacted]
40	5.4	[redacted]	[redacted]

Figure 12 Survival at different CFR levels on top of SMR (updated base case model) and detail showing duration at median survival.



Increasing the CFR reduces median survival (range: 5.4 years (40%) to 9.4 years (10%)). The probabilistic ICER is similarly affected. With an underlying SMR it ranges from [redacted] to [redacted]

We have shown using real world evidence in Section 3 above that it is highly likely for survival in the population of interest to be around 7 to 8 years. This requires a CFR of slightly above 15% and we used the Hoogendorn estimate in our modelling which meets this requirement. At committee we heard clinical opinion that the modelled median survival may be overestimated, and that survival could be somewhat shorter. The figures above illustrate that to achieve shorter survival higher CFRs are required. For example, for median survival to be 5.5 years a CFR of 40% is required on top of the underlying risk modelled using SMRs. In this case the probabilistic ICER reduces from [redacted] in the Sanofi Base case (CFR = 15.6%) to [redacted] illustrating that with worse survival in the SoC arm dupilumab could be much more cost-effective.

7. A scenario analysis applying a CFR due to exacerbations without the application of SMRs, or any other adjustment for mortality (Section 3.11 in the Draft Guidance)

In this section we discuss the implications for survival using only a CFR (Section 7.1) and provide a sensitivity analysis to account for any mortality benefit that may have been removed with the underlying SMR (Section 7.2).

The base case model uses a CFR based only on severe exacerbations, but clinicians we have spoken to, and literature precedent suggest **moderate exacerbations also contribute to mortality**. This could potentially be at a ratio of 5:1 compared to severe events. This means the model may underestimate mortality.

Without applying an SMR, the current CFR of 15.6% yields a median survival of 10.5 years which is an overestimate. We have illustrated the mortality impact using different CFRs with no underlying SMR at 5% increments and developed a scenario incorporating moderate exacerbation risk. This is supported by data from Rothnie, 2018 which shows increasing mortality with more moderate events.

Real-world data from the HES study shows a 5.6:1 ratio of moderate to severe exacerbations, **justifying a doubled CFR of 31.6%** in sensitivity analysis. This adjustment lowers median survival to 6 years, with ICERs of [redacted] /QALY (probabilistic) and [redacted] /QALY (deterministic), offering a more accurate reflection of mortality risk when SMR is excluded.

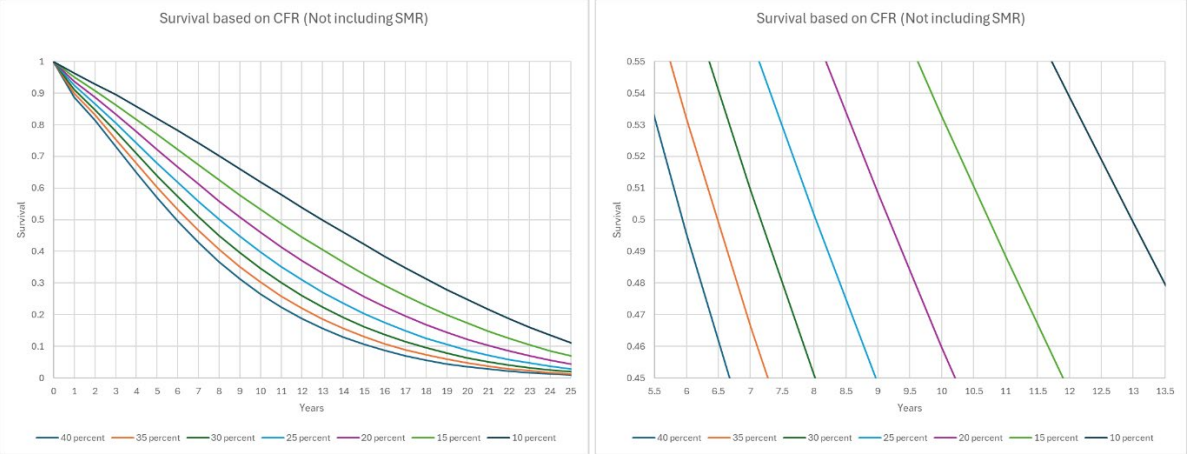
7.1. Application of different CFRs in the model with no underlying SMR

This methodology has precedent, notably in TA461 (Roflumilast) but survival in the model using the base case settings with no underlying SMR produces an estimate for median survival in the SoC arm at 10.5 years with CFR = 15.6%. For this sensitivity analysis the probabilistic ICER is [redacted] and the deterministic ICER is [redacted].

Median survival 10.5 years is too long for the population of interest indicating that an underlying SMR is required to account for all other elevated risk factors (note that the model does apply age related COPD mortality, SMRs are relative to these data). In this case probabilistic ICER has reduced from [redacted] to [redacted] because of longer residency in the less severe health states providing more life years and quality of life differential between arms despite increase in costs.

We have illustrated the impact using different CFRs with no underlying SMR at 5% increments starting from 10% in Figure 13 below.

Figure 13 Survival at different CFR levels with no underlying SMR (updated base case model) and detail showing duration at median survival.



Removing the underlying risk from an SMR increases median survival and increases the range (~6.0 years (CFR of 40%) to ~12.9 years (CFR of 10%)). (Figure 13). Similarly with no underlying SMR the ICER range is [redacted] to [redacted]. (Table 14).

Table 14 ICERS at different CFRs between 10% and 40% with NO background mortality (SMR) included.

CFR (%)	Median survival (years)	With underlying SMR	
		Probabilistic ICER	Deterministic ICER
10	12.9	[redacted]	[redacted]
15	10.7	[redacted]	[redacted]
20	9.2	[redacted]	[redacted]
25	8.0	[redacted]	[redacted]
30	7.2	[redacted]	[redacted]
35	6.5	[redacted]	[redacted]
40	5.9	[redacted]	[redacted]

7.2. Sensitivity analysis

Our base case modelling uses a CFR associated with severe exacerbations only. Clinicians have told us that moderate exacerbations also have a mortality implication, perhaps as high as 3 moderate exacerbations being equivalent to 1 severe, and so our modelling may underestimate mortality in this population. There is literature precedent to indicate that moderate exacerbations also carry a risk or mortality, albeit at a lesser rate than severe exacerbations (but still significant), and that therefore an CFR based on severe exacerbations alone conservatively estimates the impact of exacerbations (and exacerbation reduction with dupilumab versus SoC) on mortality.

In this section we consider scenarios in which there is no underlying mortality risk modelled with an SMR vs general population mortality and have shown above that the estimate for median survival in the SoC arm using the base case CFR of 15.6% is 10.5 years. This is an overestimate and so to improve the accuracy of the model using only a CFR we have developed a scenario in which the CFR is updated to include moderate exacerbations. This scenario may be appropriate as any underlying influence from moderate exacerbations that may be present in the SMR has been removed here.

The study published by Rothnie 2018 which examined mortality risk following exacerbations, has been discussed in 3.4.1 above. The risk of death following exacerbations from this study by frequency is shown in Table 15. The authors state that 5 or more moderate exacerbations may not

carry equivalent mortality risk to 1 severe exacerbation but it is clear that this risk increases in a graduated manner, meaning with every additional moderate exacerbation there is a further increase in the risk of death, and it comes close in the 5+ category. (Note there is no data for a single severe moderate exacerbation available from this study. The HR for the 1+ severe exacerbation will include more than 1 severe exacerbation AND any number of moderate exacerbations so this HR may be expected to be slightly higher than for a single prior severe exacerbation in the same period).

Table 15. Risk of death following exacerbations [Rothnie 2018]

Exacerbation category	Adjusted HR for death
None	1 (reference)
1 moderate	1.01 (0.93 to 1.11)
2 moderate	1.10 (1.03 to 1.18)
3 moderate	1.25 (1.15 to 1.36)
4 moderate	1.32 (1.20 to 1.46)
5+ moderate	1.57 (1.45 to 1.70)
1+ severe (and any moderate)	1.79 (1.65 to 1.94)

Similarly, the risk of mortality expressed as an incident rate ratio from Whittaker 22 (See above) shows that relative to no exacerbations the IRR increases with more moderate exacerbations (3+ moderate: IRR 1.32 ((1.26 – 1.39); 1 severe: 1.75 (1.66 – 1.85); 3+ severe: 2.87 (2.53 – 3.25). The 5 moderate exacerbations category is not available from Whittaker 22).

Our HES study discussed in Section 3.4.2 recorded the annual frequency of moderate and severe exacerbation in a real world cohort aligned to the inclusion criteria from BOREAS and so provides the best available evidence for the ratio of moderate to severe exacerbations in the population of interest. (See Table 16). In this study the ratio of moderate to severe exacerbations was 5.622 (2.294 / 0.408 = 5.622) meaning for every 1+ severe exacerbation there where 5.6 moderate.

Table 16. Distribution of moderate or severe exacerbation events in the population of interest

Exacerbation category	Annual rate of exacerbations, mean (95% CI)
All	2.702 (2.676, 2.729)
Moderate exacerbations	2.294 (2.270, 2.319)
Severe exacerbations	0.408 (0.398, 0.418)

In the following scenario we have made an assumption based on Rothnie that mortality risk from 5 moderate exacerbations is equivalent to 1 severe exacerbation at the upper limit. Assuming 1:5 mortality equivalence for moderate to severe and noting the same ratio from the HES study then it is not unreasonable to double the CFR used and model 31.6% CFR in sensitivity analysis as a credible upper limit for the CFR (15.6% from severe exacerbations according to Hoogendorn and an equivalent proportion due to moderate exacerbations).

Using the updated Sanofi base case with no SMR and the adjusted CFR the model estimates median survival at 6 years. For this sensitivity analysis the probabilistic ICER is [redacted] and the deterministic ICER is [redacted]

This analysis should be treated with caution as the contribution to the CFR from moderate exacerbations is uncertain.

8. Valuing COPD: Willingness to pay

We have directed our responses to analyses requests from the draft guidance to reduce uncertainty. In particular we have shown that real world survival in the population of interest is likely to be between 7 and 8 years. We have provided supportive evidence for the use of the modelling methodology incorporating a CFR and an SMR and shown how the estimate taken from Hoogendorn for the CFR is credible. There is also strong reason to believe that the treatment effect of dupilumab should persist and maybe even diverge whilst on treatment due to exacerbation reduction and by analogy to TRAVERSE and to patterns observed in ex-smokers. Furthermore, we have shown that dupilumab does reduce severe exacerbation frequency relative to current SoC and that the impact of this reduction is likely to have significant system benefits. Finally, the EAG and committee have accepted that the clinical trials were well designed and are generalisable to UK clinical practice.

We also suggest reconsideration of the issue of health inequalities, with COPD being an identified health inequalities priority of NHS England.

A low willingness to pay of £20k/QALY has been suggested in the DG due to the uncertainties identified by the committee. We have addressed these points meaning that WTP = £20k/QALY is no longer applicable. Therefore, a more suitable WTP threshold is towards the higher end of NICE's WTP range, given the increased certainty together with the recognised value that dupilumab brings to uncontrolled COPD patients and potential benefits to NHS resourcing.

9. Results from the updated economic modelling

The updated Sanofi base case includes all the EAG preferences in their base case except for the removal of the CFR. Following committee meeting 1 the preference of the committee to include the T2 modifier has been incorporated. The key changes are presented in Table 17 below.

Table 17 Updated Sanofi base case

Parameter	**Updated parameter estimate**	**Change from original Sanofi base case**	**Justification**
CFR	15.6%. Hoogendorn 2011.	No change	Inclusion of the CFR recognises the link between exacerbations and mortality and provides credible survival estimates
Adjusted Fenwick risk equation (T2 modifier)	1.52 multiplier. Fenwick FEV1 decline adjusted according to CanCOLD.	No change	Committee preference
Utility	Derived from the utility regression model including only statistically significant covariates.	Change from treatment specific utilities	Non treatment specific utility applied. Committee preference
Baseline distribution of COPD severity at start of Markov	Trial baseline distribution for SoC with trial treatment effect to inform dupilumab distribution	Change from ITT trial data at end of trials (removal of the FEV1 trial effect)	EAG preference
Non-fatal CV events	No difference between arms	Change from different rates between arms	EAG preference
% requiring nurse home administration	5%	Change from 0%	EAG preference
Follow-up appointment after	37% within 90 days	Change from 17% at 30 days	EAG preference

severe exacerbation		and 37% at 90 days	

Updated Base case results

Table 18. Updated base case results: Probabilistic

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Background Therapy	[redacted]	[redacted]	[redacted]				

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Table 19. Updated base case results: Deterministic

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Background Therapy	[redacted]	[redacted]	[redacted]				

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

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

Addendum to the Sanofi consultation response to the NICE Draft Guidance, 28th May 2025

We wish to provide additional information to support the NICE decision-making process, particularly regarding the request for additional evidence in Section 3.11 of the Draft Guidance

- Provide further evidence to support applying a CFR to account for the increased risk of mortality from exacerbations
- Provide alternative sources of evidence for the CFR
- Provide a scenario analysis applying a CFR due to exacerbations without the application of SMRs, or any other adjustment for mortality

A real-world evidence study of a cohort of 2645 physician and spirometry confirmed COPD patients, admitted consecutively with a severe exacerbation at 6 English hospitals between 2008 and 2014, has been published across 2 papers. These quantify all-cause mortality up until patient discharge (Echevaria, 2022), and subsequently over the following 90-days (Echevaria, 2017) or 365-days (Echevaria, 2022).

In Echevaria 2022 below, the inpatient all-cause mortality rate was 8.6%

Table 1 Inpatient mortality among patients with an exacerbation of COPD by eosinophil count

	All COPD exacerbation			Pneumonic exacerbation			Non-pneumonic exacerbation		
Eosinophil count	Total	Died	%	Total	Died	%	Total	Died	%
Total	2645	228	8.6	788	129	16.4	1857	99	5.3

COPD, chronic obstructive pulmonary disease.

(Source; Table 1, Echevaria 2022)

In Echevaria 2017 below, the all-cause mortality rate over the 90-days following discharge was 9.7%.

Risk	Score	Expected probability derivation cohort	Observed probability derivation cohort	Observed probability internal validation cohort	Observed probability external validation cohort	P value	Readmission or death within 90 days	Death alone within 90 days	Readmission alone within 90 days	Readmission or death within 30 days	Total (all patients)
Total			309 / 824	297 / 802	330 / 791	0.11	936	234	844	535	2417
%		37.5	37.5	37.0	41.7		**38.7**	9.7	34.9	22.1	

P value compares the three observed proportions by Fishers test (the comparison of expected to observed probabilities is shown separately by the Hosmer-Lemeshow statistic and the calibration curve).

(Source; Table E3, Echevaria 2017)

And hence the overall all-cause mortality rate for a severe exacerbation over the 90-days (including inpatient deaths) was **17.5%** ((228+234 died)÷2645). The 90-day mortality rate calculated from 2018-2020 national audit data was 11.9% (NACAP data, provided previously), but the corresponding Echevaria author has noted that national audit data will often not be physician and spirometry confirmed COPD, and so will underestimate the impact of COPD exacerbations (personal communication). The data provided in Echevaria is based on a more robust adjudication of severe exacerbation in COPD, aligned to the criteria used in the BOREAS & NOTUS studies.

In Echevaria 2022 below, the all-cause mortality rate for a severe exacerbation over 1-year (including in-patient deaths) was **29.8%**.

Table 4 1-year mortality among patients with an exacerbation of COPD by eosinophil count

Eosinophil count	1-year mortality (excluding inpatient deaths)			1-year mortality (including inpatient deaths)		
	Total	Died	%	Total	Died	%
Total	2417	560	23.2	2645	788	29.8

COPD, chronic obstructive pulmonary disease.

(Source; Table E3, Echevaria 2017)

NB: NICE may note that Echevaria 2022 also provided mortality data stratified by blood eosinophil count levels. However, these were measured during exacerbation admission and are therefore not informative of the eosinophil levels present outside of an exacerbation which are generally higher. Importantly, BOREAS and NOTUS EOS levels for screening were measured following at least a 4 week gap after an exacerbation, corresponding to the 'stable' COPD referred to below. The authors state: "In this large, multisite UK-based study, 52% of patients with severe ECOPD had very low eosinophil counts of less than 0.05×10^9 cells/L [eosinopenia] at admission. This proportion is substantially higher than what is typically seen in stable COPD patients, where the average eosinophil count is approximately 0.2×10^9 /L and far fewer patients exhibit eosinopenia"

Taking the above information into account, a valid alternative severe exacerbation case fatality rate (CFR), using relatively recent real-world data from clinically validated English COPD patients, would be 17.5% (90-day mortality). Such a CFR could be used along with SMRs to appropriately describe the mortality of COPD patients. The calculated median survival in this case is approximately **7.96 years**

Recognising that the mortality risk for exacerbations extends past 90-days, and that a high proportion of patients experience additional subsequent severe exacerbations that require re-admission (34.9% within 90 days in Echevaria 2017, above), another valid alternative severe exacerbation CFR is 29.8% (1-year mortality). In this case, such a CFR should be used alone, as addition of SMRs will introduce 'double-counting' for causes of death other than that related to exacerbations, and the calculated median survival in this case is approximately **7.17 years**.

CFR 17.5% (90-day mortality) with COPD SMR CEM Results

Table 1. Deterministic Results with 17.5% CFR (model based on the updated draft guidance CEM base case)

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Background Therapy	[redacted]	[redacted]	[redacted]				

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Table 2. Probabilistic Results with 17.5% CFR (model based on the updated draft guidance CEM base case)

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Background Therapy	[redacted]	[redacted]	[redacted]				

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

CFR 29.8% (1- year mortality) with no COPD SMR CEM Results

Table 3. Deterministic Results with 29.8% CFR (model based on the updated draft guidance CEM base case)

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Background Therapy	[redacted]	[redacted]	[redacted]				

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Table 4. Probabilistic Results with 29.8% CFR (model based on the updated draft guidance CEM base case)

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Background Therapy	[redacted]	[redacted]	[redacted]				

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

References:

Echevarria C, Steer J, Heslop-Marshall K, Stenton SC, Hickey PM, Hughes R, Wijesinghe M, Harrison RN, Steen N, Simpson AJ, Gibson GJ, Bourke SC. The PEARL score predicts 90-day readmission or death after hospitalisation for acute exacerbation of COPD. Thorax. 2017 Aug;72(8):686-693. doi: 10.1136/thoraxjnl-2016-209298. Epub 2017 Feb 24. PMID: 28235886; PMCID: PMC5537524.

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Echevarria C, Steer J, Prasad A, Quint JK, Bourke SC. Admission blood eosinophil count, inpatient death and death at 1 year in exacerbating patients with COPD. Thorax. 2023 Nov;78(11):1090-1096. doi: 10.1136/thorax-2022-219463. Epub 2023 Jul 24. PMID: 37487711.

https://thorax.bmj.com/content/thoraxjnl/78/11/1090.full.pdf?with-ds=yes

Corrections to the Sanofi consultation response to the NICE Draft Guidance:

Additionally, we need to apologise and point out two minor errors we have since identified in our original response to the Draft Guidance, corrected in highlighted text below:

1. **1.1. Reduction in severe exacerbations observed in the clinical trials**, page 7, point B;
   "In a post-hoc analysis, dupilumab delayed the time to first severe exacerbation compared to SoC by 38.9%, with a significant p value of 0.0160."
   The highlighted numbers are however correct in Table 1.
2. **7.1. Application of different CFRs in the model with no underlying SMR**, page 41, Table 14;

CFR (%)	Median survival (years)	Without underlying SMR	
		Probabilistic ICER	Deterministic ICER
10	12.9	[redacted]	[redacted]
15	10.7	[redacted]	[redacted]
20	9.2	[redacted]	[redacted]
25	8.0	[redacted]	[redacted]
30	7.2	[redacted]	[redacted]
35	6.5	[redacted]	[redacted]
40	5.9	[redacted]	[redacted]

Appendix A. HES database study

The aim of this observational study was to extract a cohort based on the inclusion and exclusion criteria for the BOREAS clinical trial from the liked hospital episodes statistics (HES), Clinical Practice Research Database (CPRD) Aurum, and Office for National Statistics (ONS) data to assess rates of exacerbation (moderate and or severe) over the study period to provide baseline rates for the economic modelling. Limited mortality data was also collected.

Study design

Historical cohort study (using prior prospectively collected data)

Setting

Linked, de-identified, routinely collected electronic healthcare record data were used from the HES dataset. Study start was the January 1st 2010 and end was August 31st 2021. The study population was people with a validated COPD diagnosis code in CPRD who were over the age of 40 (as per BTS guidance on diagnosing patients with COPD), eligible for HES, ONS, and Index of multiple deprivation (IMD) linkage, had a smoking history (i.e., current or ex-smokers), had continuous registration at a General Practice (GP) with acceptable data in the year before index, and had at least one day of follow-up time before experiencing the outcome of interest.

Subjects

Inclusion criteria

People with COPD, defined as per validated definition who aligned with the BOREAS dupilumab clinical trial population as closely as could be determined from health electronic records.

- Current or former smokers
- 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.
- Evidence of chronic bronchitis
- Background triple therapy (ICS + LABA + LAMA)
- Evidence of Type 2 inflammation: Patients with blood eosinophils ≥300 cells/microliter

Exclusion criteria

- COPD diagnosis for less than 12 months
- 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.
- Exacerbation of COPD within 4 weeks of start of follow up
- History of, or planned pneumonectomy or lung volume reduction surgery.
- Diagnosis of α-1 anti-trypsin deficiency.

Variables

Controlled COPD

To align with the BOREAS population but with no moderate or severe exacerbations in the past 12 months while on triple therapy.

Uncontrolled COPD

To align with the BOREAS population but two or more moderate or one or more severe exacerbation within the past 12 months while on triple therapy.

Outcomes

- Rates of exacerbation; moderate and or severe exacerbation over the study period
- Mortality.

A moderate exacerbation is defined as a COPD-related primary care visit with either a code for exacerbation diagnosis (including LRTI read codes) and/or prescription for respiratory antibiotics and systemic corticosteroids (oral) not on the same day as an annual review used in the management of acute worsening of COPD symptoms within 7 days of the Adverse Event of COPD (AECOPD) or Lower Respiratory Tract Infection (LRTI) code. This definition has previously been validated in CPRD.

A severe exacerbation is defined as a hospitalization with a code for acute respiratory event including COPD or bronchitis as a primary diagnosis or a secondary diagnosis of COPD following previous validation in HES.

An event within a 14-day time period is defined as the same event with the most severe level recorded determining severity.

Data sources and measurement

CPRD Aurum, HES and Office for National Statistics (ONS) mortality data were used. Aurum contains anonymised, longitudinal medical records from patients registered with participating primary care practices across the UK and is representative of the general UK population in terms of age and sex. All GPs included in this study had quality checked

data as defined by CPRD (i.e. Up To Standard, UTS is the date when data collected from each practice are deemed to have adequate quality for research).

Data in the CPRD Aurum databases contains:

- patient demographics,
- clinical diagnoses,
- consultations,
- primary care prescription medications,
- laboratory tests, and
- specialist referrals

Data from CPRD Aurum were linked to HES APC data at the patient level to ascertain secondary care in-patient information on exacerbations and hospitalisations. Data were also be linked to ONS data to determine deaths and cause of deaths and the Index of Multiple Deprivation (IMD) to determine socioeconomic status.

bias

Specific SNOMED-CT codes were chosen to maximize the sensitivity of diagnosing COPD and exacerbations based on previous validation studies. We are aware there may have been misdiagnosis and misclassification of COPD and exacerbations of COPD. Ultimately, however, we are limited by the acumen of the reviewing clinician recording the diagnosis.

We have not included any cells with counts less than five due to anonymity concerns.

We undertook complete case analysis and there was no multiple imputation.

Study size

Using the power calculation from the BOREAS trial, it was 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).

Statistical methods

Analyses were conducted in STATA statistical software, version 17, and/or R. All executable files that are used to provide data tables and statistical outputs were stored in a study specific area by the researcher working on the project with clear annotation showing the sequence in which they can be used to replicate results, as per standard practice.

Main summary measures

Summary statistics are provided. Continuous measures have been described using means and standard deviations or medians and interquartile ranges (as appropriate). Categorical measures have been reported using frequencies and proportions. Count variables where

appropriate are expressed as rates per person-year. Data have been described for the controlled and uncontrolled groups for each study population as appropriate.

Exacerbation rates

Negative Binomial regression models were used to predict the adjusted annual rate of exacerbations. A negative binomial regression was fitted including log-transformed observation duration (i.e., exposure) in years as an offset variable. The annual rate was defined as the count of exacerbation events divided by person-years of follow-up duration the year, thus including the latter as an offset variable facilitates the estimation of adjusted annual rates using the *nbreg* command.

Frequency of moderate and severe exacerbations

The number and percentage of exacerbations (moderate vs. severe) were summarized for the whole COPD cohort and controlled and uncontrolled population. Severe exacerbations were further stratified by fatal vs. non-fatal event counts and proportions. The annual rate of exacerbations was calculated as the total number of exacerbations divided by the total person-years.

Participants

Overall, there were 10,778 people in the cohort, 4,398 with controlled and 3,747 with uncontrolled COPD.

Results

Descriptive data

The baseline characteristics are described in Table 1.

Table 1: Baseline characteristics

	COPD Cohort (n=10,778)		Controlled COPD (n=4398)		Uncontrolled COPD (n=3747)	
Age	n	%	n	%	n	%
Mean (SD)	69.88	10.37	69.75	10.21	69.97	10.54
Median (Range)	70	41-99	70	41-96	70	41-99
Gender						
Male	6576	61.01	2870	65.26	2099	56.02
Female	4202	38.99	1528	34.74	1648	43.98
Region						
North East	544	5.05	209	4.75	212	5.66
North West	2961	27.47	1139	25.9	1054	28.13
Yorkshire and The Humber	411	3.81	173	3.93	149	3.98
East Midlands	226	2.1	97	2.21	69	1.84

West Midlands	1709	15.86	713	16.21	604	16.12
East of England	393	3.65	162	3.68	125	3.34
London	1279	11.87	575	13.07	421	11.24
South East	2042	18.95	828	18.83	681	18.17
South West	1213	11.25	502	11.41	432	11.53
Quintile of 2019 Index of Multiple Deprivation						
1	1337	12.4	556	12.64	447	11.93
2	1798	16.68	740	16.83	629	16.79
3	1937	17.97	817	18.58	643	17.16
4	2427	22.52	992	22.56	821	21.91
5	3266	30.3	1287	29.26	1203	32.11
Missing	13	0.12	6	0.14	4	0.11
Depression	2879	26.71	1057	24.03	1107	29.54
Anxiety	2107	19.55	781	17.76	781	20.84
Gastro-oesophageal reflux disease	2239	20.77	806	18.33	879	23.46
Acute coronary syndrome	1357	12.59	524	11.91	500	13.34
Heart failure	1298	12.04	457	10.39	506	13.5
Stroke	967	8.97	390	8.87	354	9.45
Atopy	3609	33.48	1399	31.81	1307	34.88
Nasal Polyps	243	2.25	103	2.34	92	2.46
Venous thromboembolism	677	6.28	257	5.84	267	7.13
Smoking status at start of follow-up						
Ex-smoker	5230	48.52	2071	47.09	1859	49.61
Current smoker	5548	51.48	2327	52.91	1888	50.39
MRC dyspnoea scale						
2	3786	35.13	1704	38.74	1135	30.29
3	4017	37.27	1632	37.11	1377	36.75
4	2437	22.61	892	20.28	977	26.07
5	538	4.99	170	3.87	258	6.89
GOLD Stage						
GOLD 2	6269	58.16	2670	60.71	2074	55.35
GOLD 3	4509	41.84	1728	39.29	1673	44.65
BMI						
Underweight	583	5.41	240	5.46	216	5.76
Normal	3356	31.14	1355	30.81	1179	31.47
Overweight	3182	29.52	1330	30.24	1090	29.09
Obese	3237	30.03	1306	29.7	1110	29.62
Missing	420	3.9	167	3.8	152	4.06
Moderate AECOPDs in year prior to start of follow-up						
0	4900	45.46	4398	100	502	13.4

1	2633	24.43	0	0	0	0
2	1432	13.29	0	0	1432	38.22
3	787	7.3	0	0	787	21
4	444	4.12	0	0	444	11.85
5	252	2.34	0	0	252	6.73
6	154	1.43	0	0	154	4.11
7	64	0.59	0	0	64	1.71
8	44	0.41	0	0	44	1.17
9	29	0.27	0	0	29	0.77
>=10	39	0.36	0	0	39	1.04
Severe AECOPDs in year prior to start of follow-up						
0	9258	85.9	4398	100	2620	69.92
1	1181	10.96	0	0	872	23.27
2	223	2.07	0	0	168	4.48
3	78	0.72	0	0	57	1.52
4	22	0.2	0	0	18	0.48
>=5	16	0.15	0	0	12	0.32
<0.5 Giga/L	8434	78.25	3504	79.67	2827	75.45
>=0.5 Giga/L	2344	21.75	894	20.33	920	24.55

Calculation of the proportion of patients with 1 or more severe exacerbation at baseline

	Number of severe exacerbations in the uncontrolled cohort	Calculated number of patients
0	2620	N/A
1	872	872
2	168	168/2 = 84
3	57	57/3 = 19
4	18	18/4 = 4.5
>=5	12	12/6 = 2.4
Total number of patients (to 0 dp)		982

There were 3747 patients in the uncontrolled cohort (population of interest) of whom 982 had 1 or more severe exacerbations. This equates to 26.2% of patients with a severe exacerbation.

Outcome data

Table 2 shows the distribution of moderate or severe exacerbation events is in table 3. The proportion of people who died in each group is in table 5.

Table 2: Distribution of moderate or severe exacerbation events

Exacerbation	COPD Cohort (n=10,778)	Controlled COPD (n=4398)	Uncontrolled COPD (n=3747)
Total No. of exacerbations	85,719	23,874	41,144
Moderate exacerbations, n(%)	71, 142 (83.0%)	19159 (80.3%)	34933 (84.9%)
Severe exacerbations, n(%)	14, 577 (17.0%)	4715 (19.7%)	6211 (15.1%)
Fatal exacerbation, n(%)	1431	503	601
Total person-years of follow-up	47,210.53	20, 203.09	15,225.07
Annual rate of exacerbations, mean (95% CI)	1.816 (1.804, 1.828)	1.182 (1.167, 1.197)	2.702 (2.676, 2.729)
Moderate exacerbations	1.507 (1.500, 1.518)	0.948 (0.935, 0.961)	2.294 (2.270, 2.319)
Severe exacerbations	0.309 (0.304, 0.314)	0.233 (0.227, 0.240)	0.408 (0.398, 0.418)
Fatal exacerbation	0.030 (0.029, 0.032)	0.025 (0.023, 0.027)	0.039 (0.036, 0.043)

Table 5: Cause of death

Cause of death	COPD Cohort (n=10,778)		Controlled COPD (n=4398)		Uncontrolled COPD (n=3747)	
	n	%	n	%	n	%
Total deaths	4271	39.63	1706	38.79	1522	40.62
Exacerbation related	1431	13.28	503	11.44	601	16.04
CV related	870	8.07	344	7.82	302	8.06
Non-exacerbation and non-CV related	1966	18.24	856	19.46	618	16.49

Discussion

People with uncontrolled disease were of similar age and had a similar regional distribution than those with controlled disease. A slightly higher proportion were female with uncontrolled compared with controlled disease. The distribution of socioeconomic status was similar between the two groups, as were the proportions of most co-morbidities. Reflux, and some cardiovascular risk factors were slightly more common in the uncontrolled group, and they tended to be more symptomatic with higher MRC dyspnea scores and a higher proportion with GOLD 3 compared with GOLD 2 disease. BMI was similar across groups and as per the definition of controlled an uncontrolled, there were more exacerbations in those who were uncontrolled.

With respect to outcome events, there were similar proportions of people with moderate and severe exacerbation events in both the controlled and uncontrolled groups. The annual rate of exacerbations was higher in the uncontrolled group and the rate of fatal exacerbations, although small, higher in the uncontrolled group.

Limitations

We were unable to include all of the variables of interest due to lack or recording in primary care and imputation of variables was not appropriate as they were not missing at random. The outcomes are not clinically meaningful or interpretable in their current form as they are for a DES model.

Generalizability

This interpretation is limited to people with COPD defined using routinely collected electronic healthcare record data meeting the BOREAS inclusion and exclusion criteria as closely as possible.

Conclusion

There were similar proportions of people with moderate and severe exacerbation events in both the controlled and uncontrolled groups. The annual rate of exacerbations was higher in the uncontrolled group and the rate of fatal exacerbations, although small, higher in the uncontrolled group.

Appendix B. French SNDS database study

Title

Burden of Chronic Obstructive Pulmonary Disease (COPD) Uncontrolled Under Triple Therapy in France – BREATH Study

Aim

To compare the mortality of COPD patients with exacerbation(s) on triple therapy to:

- The overall French population (2015–2021)
- COPD patients without exacerbation on triple therapy (2015–2021)

Study Design

A retrospective longitudinal cohort study based on the Système National des Données de Santé (SNSD), which translates to National Health Data System database. This study described the COPD burden according to treatment lines, patients' pathways, costs and mortality associated with COPD in real-life in France. Patients treated for COPD by triple therapy in 2015 were included in the study. Five-year retrospective data were extracted from the SNDS for each patient to validate the diagnosis of COPD and associated comorbidities.

Inclusion period: from 01/01/2015 up to 31/12/2015

The index date was defined as the 91st day of triple therapy exposure in the inclusion period.

Follow-up period: from the index date until:

- Death
- The end of the study period (31st December 2021)
- Date of last healthcare consumption before at least 2 years without any other consumption.

Follow-back period: from the index date down to 01/01/2010

Data Source

The SNDS contains individual-level data for outpatient and private healthcare facilities health expenditure billing and reimbursement purposes (DCIR [Outpatient healthcare consumption data]), linked to the hospitalization database (PMSI [hospital discharge database]) with a unique, anonymous identifier, the Social Security Number (NIR). Therefore, it encompasses anonymous, individual-level data for all healthcare claims for more than 99% of the population residing in France, regardless of the insurance scheme, i.e. close to 65 million people.

Study populations

Population A: COPD Patients on Triple Therapy

Inclusion Criteria

Individuals were included in Population A if they met all of the following conditions:

- Possessed a unique Social Security Number (NIR) in the SNDS database.
- Were aged 40 years or older at the index date.
- Received triple therapy in 2015, defined as the combination of:
    - Long-acting β2-agonist (LABA),
    - Long-acting muscarinic antagonist (LAMA),
    - Inhaled corticosteroids (ICS),
- Maintained continuous exposure to triple therapy for at least 90 consecutive days prior to the index date.

Exclusion Criteria

None specified.

Subgroups Within Population A

Population A was stratified into two subgroups based on exacerbation history:

1. Population A1: Main Population of Interest (Uncontrolled COPD)
    - Patients from Population A who experienced:
        - At least one severe exacerbation or two moderate exacerbations in the 12 months preceding the index date.
        - At least one exacerbation (of any severity) must have occurred during the period of triple therapy.
        - A minimum interval of one month was required between the initiation of triple therapy and the first recorded exacerbation.
2. Population A2: Comparator Group (Controlled COPD)
    - Patients from Population A who did not meet the criteria for Population A1.

Population B: General Population Comparator

A random sample of 1 million individuals was selected from the SNDS database, representing the general French population in 2015. This sample was matched to Population A based on baseline demographic characteristics to serve as a comparator group for mortality analysis.

Outcomes

- **Primary:** Mortality comparison between uncontrolled COPD patients and the general population
- **Secondary:** Mortality comparison between uncontrolled and controlled COPD patients

Statistical analysis

General considerations
Continuous, quantitative, variable summaries included: the number of patients (N) (with non-missing values), mean, standard deviation, median, minimum and maximum, 1st, and 3rd quartiles. Given the structure of the database, the expected number of missing values was extremely low, if not negligible. However, where necessary, this number and proportion of missing values were described.

Categorical, qualitative, variables summaries included the frequency and percentage of patients per category. The denominator for percentage calculations was based on the number of observed data unless otherwise specified. If appropriate, categories were sorted by descending frequency for ease of reading.

All applicable statistical tests were two-sided and were performed using a 5% significance level. All confidence intervals presented were 95% and two-sided.

No imputation for missing values was performed. For all outcomes, missing data were quantified in terms of the number of unique patients with missing data. Patients with missing data were assigned to unknown categories; means and medians only included patients with at least one record for the characteristic or event for the outcome.

Matching strategies
In order to compare groups of COPD patients with triple therapy and exacerbation (population A1) to overall population (population B) and to COPD patients with triple therapy and without exacerbation (population A2), 2 matching procedures were implemented.

Propensity score (PS)-matching was performed. The estimation of propensity score was performed to control for confounders in the dataset: population A1 versus population B and versus population A2. Propensity scores were estimated by logistic regression analyses that incorporate potential disease predictors as independent variables and presence of disease as the dependent variable.

Covariates in the logistic regression model were include variables:

- Matching 1: Population A1 vs population B:
    - Age (40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, 85-89, 90+)
    - Sex
    - Density of pulmonologist ([0 ; 1.30[, [1.30 ; 1.75[, [1.75 ; 2.15[, [2.15 ; + [ )
    - Detail conditions of Charlson Comorbidity Index (except COPD):
        - Myocardial infarction
        - Congestive heart failure
        - Peripheral vascular disease
        - Cerebrovascular disease

        - Dementia
        - Connective tissue disease
        - Ulcer disease
        - Hemiplegia
        - Moderate or severe renal disease
        - HIV-AIDS
        - Liver disease
        - Diabetes
        - Tumor

- Matching 2: Population A1 vs population A2:
    - Age (40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, 85-89, 90+)
    - Sex
    - Density of pulmonologist ([0 ; 1.30[, [1.30 ; 1.75[, [1.75 ; 2.15[, [2.15 ; + [ )
    - Detail conditions of Charlson Comorbidity Index (except COPD):
        - Myocardial infarction
        - Congestive heart failure
        - Peripheral vascular disease
        - Cerebrovascular disease
        - Dementia
        - Connective tissue disease
        - Ulcer disease
        - Hemiplegia
        - Moderate or severe renal disease
        - HIV-AIDS
        - Liver disease
        - Diabetes
        - Tumor
    - Comorbidities (Asthma, Pneumopathy, Anxiety / Depression, Osteoporosis, Sleep disorders / sleep apnea syndrome, Overweight, Undernourishment).
    - Daily Polypharmacy Possession Ratio (DPPR): Yes/No for good adherence (≥80%)

Interactions and nonlinear terms of the variables were not considered. Probability (propensity score) to have COPD with triple therapy and exacerbation (matching 1) or exacerbation (matching 2) was obtained for each patient. The common support of propensity scores was checked to ensure good matching, aiming to find for each patient of population A1, at least one participant of the control group with the same characteristics (propensity score). After estimating the propensity score, propensity score matching was performed at ratios of 1:2 for matching 1 and 1:1 for matching 2, without replacement. Caliper-based nearest neighbour matching was used with a caliper defined as 0.2 of the log of the variance of the propensity score. Patients of population A1 excluded due to an absence of suitable matches were described. Balances of baseline variables between populations after matching were evaluated by computing the absolute standardized differences for all components of the propensity score. A threshold of 0.1 was used to determine an imbalance; therefore, a standardized difference < 10% was considered acceptable.

Primary objective

Mortality analyses
The overall survival curve was estimated using the Kaplan-Meier estimation method with maximal follow-up, which was also used to quantify the median survival time, restricted mean survival time, q1, and q3 of follow-up duration. Results were depicted graphically by Kaplan-Meier curves, with the number of patients still at risk tabulated below the curves at different times (1 year, 2 years, etc.). The proportion of patients not experiencing the event at one and two years after the index date was estimated using Kaplan-Meier estimates and reported alongside the two-sided 95% confidence intervals. The Greenwood method was used when calculating confidence intervals.

The time to event included the index date and event date. That is, time to event equaled (event date − index date) + 1. Similarly, if no event was observed in the follow-up period, the time to event equaled (end of follow-up period for the patient – index date) + 1.

The log-rank test was used to compare Kaplan-Meier curves (A1 vs B; A1 vs A2).

Results

Study Cohort

A total of 302,984 patients receiving triple therapy for COPD in 2015 were identified. Of these, 186,963 patients met the inclusion criteria for Population A (COPD patients exposed to triple therapy for more than three months). This population was further stratified into:

- Population A1 (Uncontrolled COPD): 39,847 patients with ≥1 severe or ≥2 moderate exacerbations in the 12 months preceding the index date, with at least one occurring during triple therapy.
- Population A2 (Controlled COPD): 147,116 patients who did not meet the criteria forA1.
- A control group (Population B) of 517,133 individuals was randomly sampled from the general French population in 2015, matched on baseline characteristics.

Figure 1: Flowchart of the selection of the population A

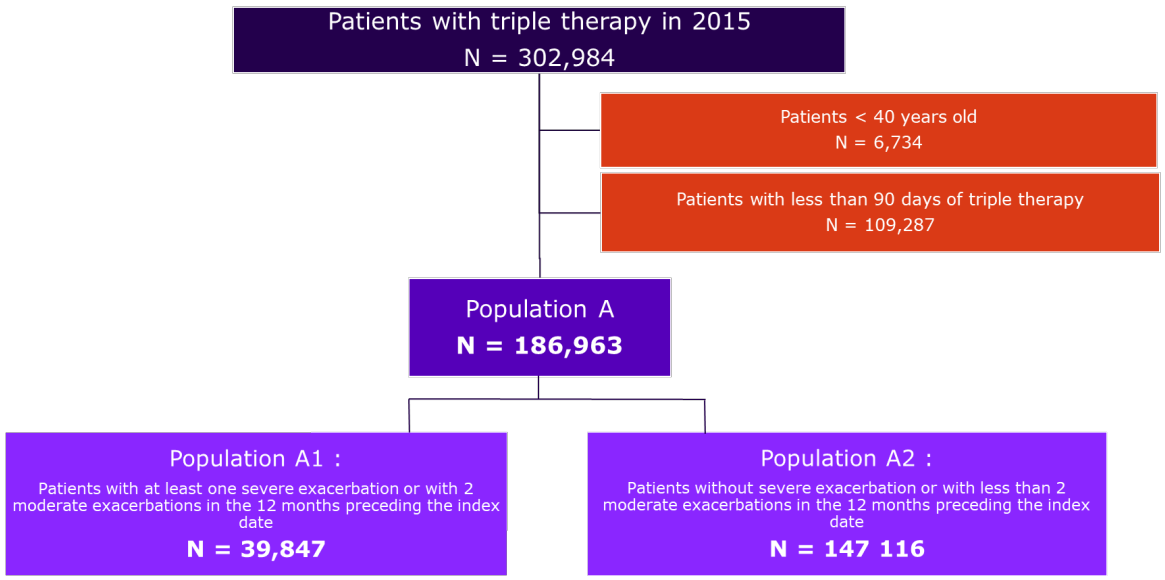
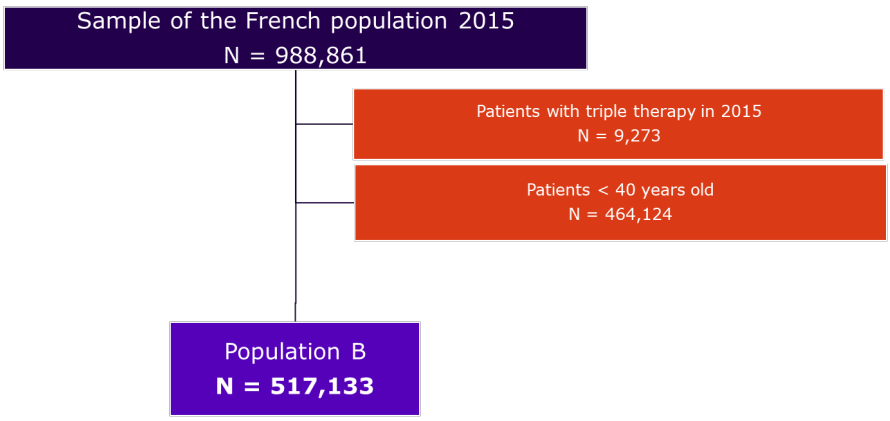


Figure 2: Flowchart of the selection of population B



Demographic characteristics at baseline, before matching

Before matching, the population A has a higher percentage of males (63.17%) compared to population B (47.24%). And the mean age of population A was higher (69.32 years) than in population B (60.55 years). Both populations had a similar mean density of pulmonologists per 100,000 inhabitants, with Population A at 1.87 (±0.80) and Population B at 1.80 (±0.78).

Comparing population A1 and A2, both subpopulations had a similar gender distribution, with a slightly higher percentage of males in Population A2 (63.82%) compared to Population A1 (60.76%). The mean age was almost identical between the two subpopulations, with Population A1 at 68.88 years and Population A2 at 69.44 years. The density of pulmonologists was also similar with Population A1 having a slightly higher mean density (1.90 (±0.80)) compared to Population A2 (1.87 (±0.80) (Table 1).

Table 1: Demographic characteristics and baseline values of the patients

Variable	Indicator	Population A	*Population A1*	*Population A2*	Population B
Number of individuals	Total	186,963	*39,847*	*147,116*	517,133
Gender	Male	118,096 (63.17%)	*24,210 (60.76%)*	*93,886 (63.82%)*	244,275 (47.24%)
	Female	68,867 (36.83%)	*15,637 (39.24%)*	*53,230 (36.18%)*	272,858 (52.76%)
Age in years	N	186,963	*39,847*	*147,116*	517,133
	Mean (±SD)	69.32 (±11.54)	*68.88 (±11.43)*	*69.44 (±11.57)*	60.55 (±13.89)
	Min; Max	40.00; 107.00	*40.00; 104.00*	*40.00; 107.00*	40.00; 120.00
	Median (Q1; Q3)	69.00 (61.00; 78.00)	*69.00 (61.00; 78.00)*	*69.00 (61.00; 78.00)*	59.00 (49.00; 70.00)
Density of pulmonologists per 100.000 inhabitants / County	Missing	257	*62*	*195*	18,402
	N	186,706	*39,785*	*146,921*	498,731
	Mean (±SD)	1.87 (±0.80)	*1.90 (±0.80)*	*1.87 (±0.80)*	1.80 (±0.78)
	Min; Max	0.00; 4.21	*0.00; 4.21*	*0.00; 4.21*	0.00; 4.21

	Median (Q1; Q3)	1.75 (1.31; 2.18)	*1.76 (1.40; 2.29)*	*1.75 (1.31; 2.18)*	1.74 (1.28; 2.14)

Inclusion characteristics at baseline, before matching

Population B has a longer follow-up duration (6.29 years (±1.77), with a median of 7.00 years) compared to Population A (5.43 years (±2.05), with a median of 6.51 years). And the follow-up duration was similar between Population A1 (5.14 years (±2.23), with a median of 6.41 years) and A2 (5.51 years (±2.00), with a median of 6.53 years). Population A1 has a higher death rate (44.68%) than Population A2 (36.25%), and then Population B (10.95%). The majority of Population B's cohort ended follow-up because of the end of the study period (82.68%), which was higher than Population A2 (62.57%), and Population A1 (54.33%). Population B had a higher percentage of individuals lost during follow-up (6.37%) compared to other populations (around 1% each) (*Table 2*).

Table 2: Inclusion patient's characteristics

Variable	Indicator	Population A	Population A1	Population A2	Population B
Number of individuals	Total	186,963	*39,847*	*147,116*	517,133
Follow-up duration (in years)	N	186,963	*39,847*	*147,116*	517,133
	Sum	1,015,389.91	*204,847.34*	*810,542.57*	3,252,676.77
	Mean (±SD)	5.43 (±2.05)	*5.14 (±2.23)*	*5.51 (±2.00)*	6.29 (±1.77)
	Min; Max	0.00; 7.00	*0.00; 7.00*	*0.00; 7.00*	0.00; 7.00
	Median (Q1; Q3)	6.51 (4.16; 7.00)	*6.41 (3.27; 6.99)*	*6.53 (4.44; 7.00)*	7.00 (7.00; 7.00)
Cause of end of follow-up	Death	71,136 (38.05%)	*17,803 (44.68%)*	*53,333 (36.25%)*	56,648 (10.95%)
	End of follow-up	113,701 (60.81%)	*21,649 (54.33%)*	*92,052 (62.57%)*	427,566 (82.68%)
	Lost during follow-up	2,126 (1.14%)	*395 (0.99%)*	*1,731 (1.18%)*	32,919 (6.37%)

Medical history

By design, in Population A1, 100% of Population A1 had an exacerbation in the year before inclusion, indicating a high-risk group. The mean number of moderate exacerbations during the follow-back period was 9.51 (±8.19), which is significantly higher than the other populations. 87.61% had a moderate exacerbation, and 34.75% had a severe exacerbation in the year before inclusion, both of which are considerably higher than the other populations. In Population A2, a smaller proportion, 30.84%, had an exacerbation in the year before inclusion. The mean number of moderate exacerbations during the follow-back period was 3.62 (±3.37), which was lower than Population A1. 28.61% had a moderate exacerbation, and only 3.86% had a severe exacerbation in the year before inclusion (*Table 3*).

Table 3: Patient's exacerbation history

Variable	Indicator	Population A	Population A1	Population A2	Population B
Number of individuals	Total	186,963	*39,847*	*147,116*	517,133
Patient with exacerbation during the year before inclusion	Yes	85,223 (45.58%)	*39,847 (100.00%)*	*45,376 (30.84%)*	0 (.%)
Number of moderate exacerbations during follow-back period per patient	Mean (±SD)	5.22 (±5.77)	*9.51 (±8.19)*	*3.62 (±3.37)*	. (±.)
	Min; Max	1.00; 135.00	*1.00; 135.00*	*1.00; 88.00*	. ; .
	Median (Q1; Q3)	3.00 (2.00; 7.00)	*7.00 (4.00; 12.00)*	*3.00 (1.00; 5.00)*	. (.; .)
Patient with moderate exacerbation during the year before inclusion	Yes	77,001 (41.19%)	*34,911 (87.61%)*	*42,090 (28.61%)*	0 (.%)
Number of moderate exacerbations during the year before inclusion per patient	Mean (±SD)	2.15 (±1.82)	*3.22 (±2.14)*	*1.27 (±0.75)*	. (±.)
	Min; Max	1.00; 30.00	*1.00; 30.00*	*1.00; 18.00*	. ; .
	Median (Q1; Q3)	2.00 (1.00; 3.00)	*3.00 (2.00; 4.00)*	*1.00 (1.00; 1.00)*	. (.; .)
Patient with severe exacerbation during the year before inclusion	Yes	19,530 (10.45%)	*13,848 (34.75%)*	*5,682 (3.86%)*	0 (.%)
Number of severe exacerbations during the year before inclusion per patient	Mean (±SD)	1.43 (±0.94)	*1.52 (±1.05)*	*1.20 (±0.56)*	. (±.)
	Min; Max	1.00; 22.00	*1.00; 22.00*	*1.00; 11.00*	. ; .
	Median (Q1; Q3)	1.00 (1.00; 2.00)	*1.00 (1.00; 2.00)*	*1.00 (1.00; 1.00)*	. (.; .)

Matching process

Matching A1 and B

Before the matching, Population A1 consisted of 39,847 patients, and Population B had a significantly larger pool of 517,133 patients. After the matching process was completed, the number of patients in Population A1 was reduced to 35,870, and the matched Population B was double that number, at 71,740 (according to the targeted matching ratio of 1:2). This indicated that 3,977 patients from Population A1 were excluded during the matching process to achieve the desired ratio (*Table 4*).

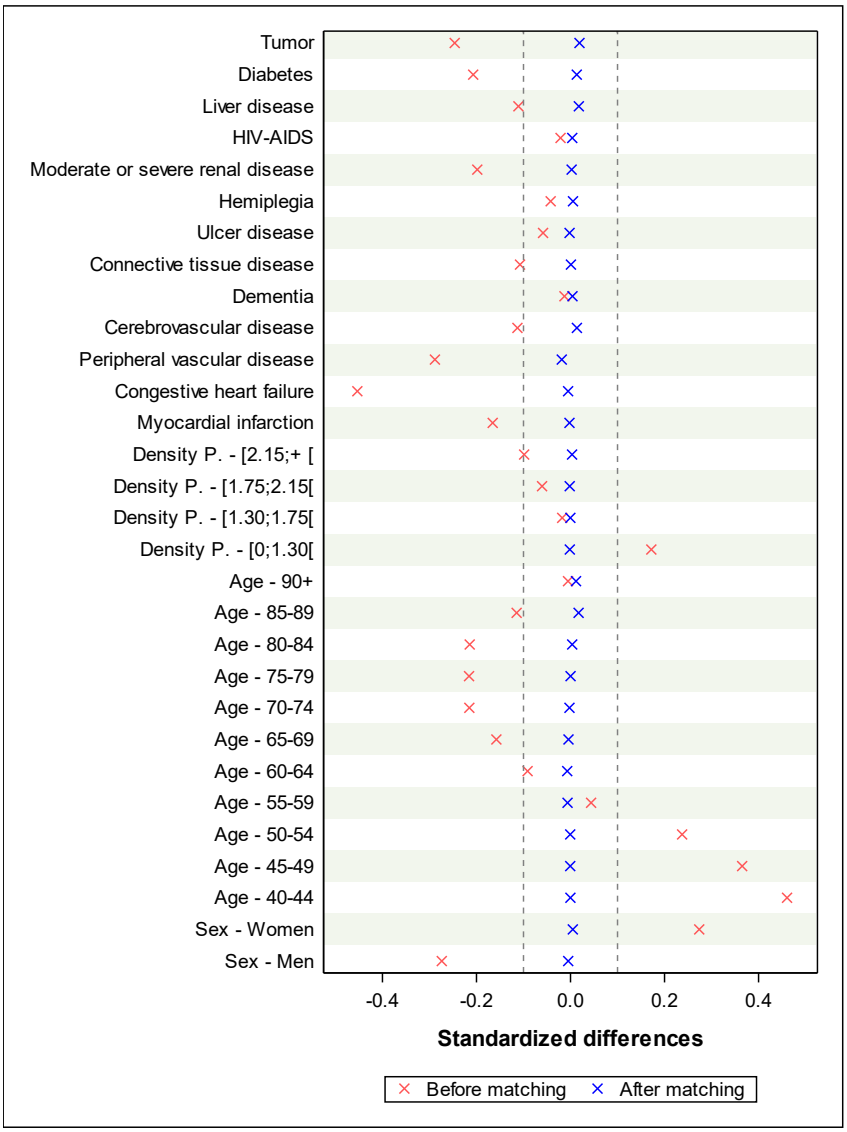
Table 4: Number of patients matched between population A1 and B with a 1:2 matching ratio

	Before matching		After matching		
	Population A1	Population B	Population A1	Population B	Population A1 excluded
N	39,847	517,133	35,870	71,740	3,977

Before the matching, the standardized differences for most conditions and demographics were more dispersed, indicating a greater imbalance between the populations being compared. After matching, the standardized differences for all listed categories were

reduced, signifying that the matching process successfully minimized the disparities between the groups (*Figure 3*).

Figure 3: Standardized differences between Population A1 and Population B with a 1:2 matching ratio



Matching A1 and A2

Before matching, Population A1 had 39,847 patients, while Population A2 had a larger number of 147,116 patients. After the matching was completed, the number of patients

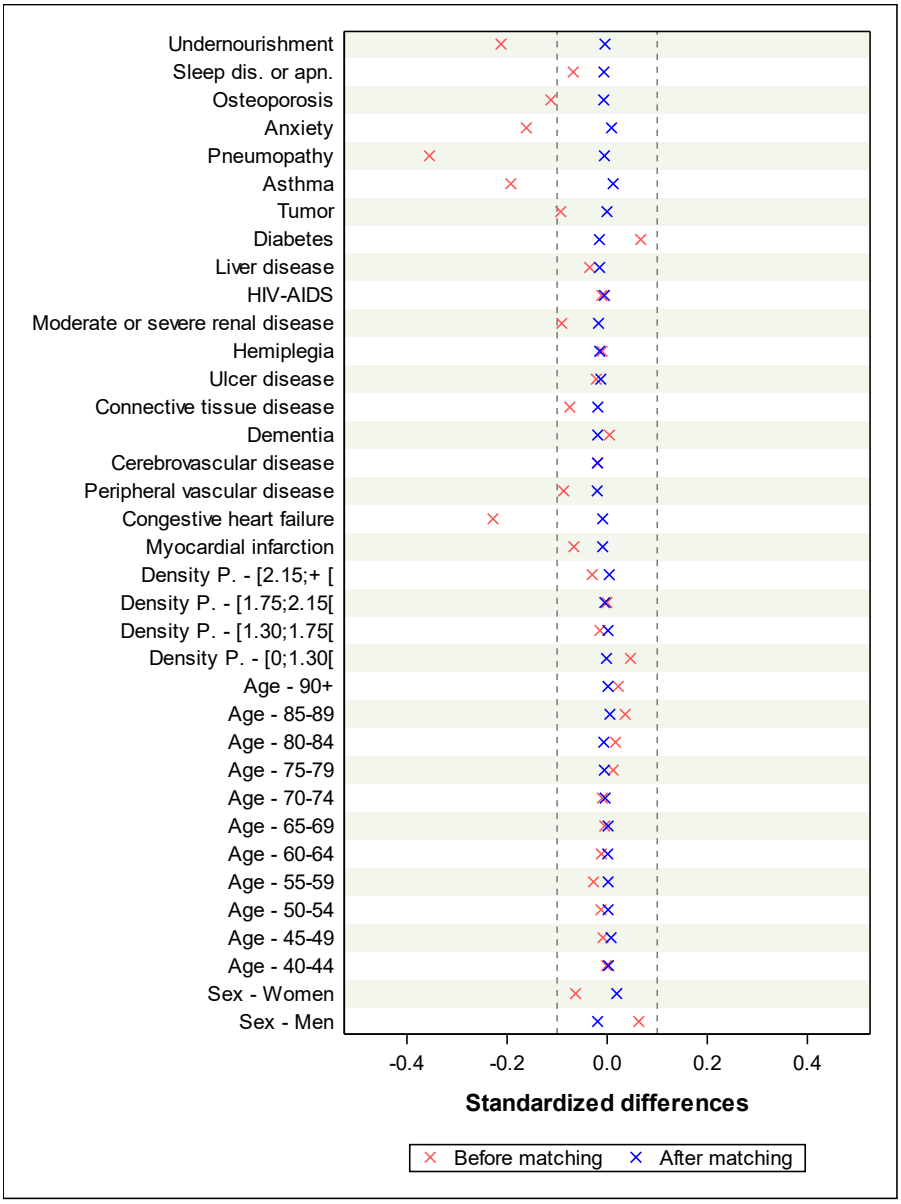
in both Population A1 and A2 was equalized to 39,709. This resulted in the exclusion of 138 patients from Population A1 to achieve the 1:1 matching ratio (Table 5).

Table 5: Number of patients matched between population A1 and A2 with a 1:1 matching ratio

	Before matching		**After matching**		
	Population A1	Population A2	Population A1	Population A2	Population A1 excluded
N	39,847	147,116	39,709	39,709	138

Before the matching, the standardized differences were more dispersed in particular for pneumopathy and congestive heart failure, indicating an imbalance between the populations being compared. After matching, the standardized differences for all listed categories were reduced, signifying that the matching process successfully minimized the disparities between the groups (Figure 4).

Figure 4: Standardized differences between Population A1 and Population A2 with a 1:1 matching ratio



Survival analysis, after matching

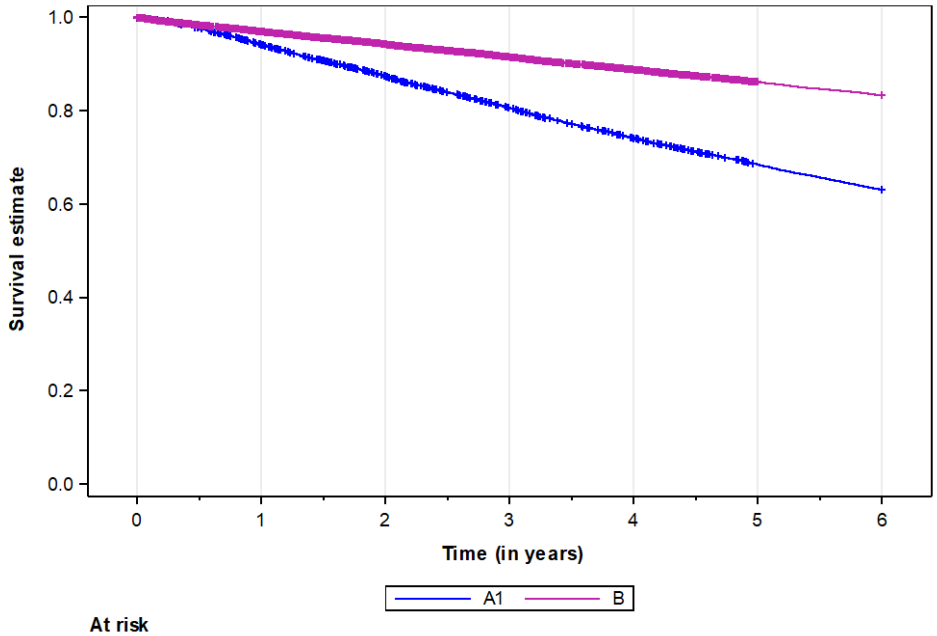
Survival of population A1 vs population B

For population A1, there was a total of 35,870 individuals, among which 13,159 events were observed. The calculated restricted mean survival time for this population was 4.86 years (±0.01). As in the previous table, the median survival time was not reached, indicating that more than half of the individuals were still alive at the end of the study, and the 95% confidence interval for the median was not provided.

For population B, the total number of individuals was 71,740, with 11,589 events observed. The restricted mean survival time for this population was slightly higher at 5.49 years (±0.01). Similar to population A1, the median survival time was not reached.

When comparing the restricted survival time distribution between population A1 and population B, it was found that population A1 had a substantially higher risk of death with a hazard ratio (HR) of 2.508 (95% CI: 2.446 to 2.572) compared to population B. This difference was highly statistically significant with a p-value of less than 0.0001, indicating a considerable discrepancy in survival outcomes between the two populations (*Figure 5*, *Table 6*).

Figure 5: Kaplan Meier modeling of survival in population A1 and B



At risk							
A1	35,870	33,711	31,238	28,714	26,357	24,275	22,368
B	71,740	68,368	65,991	63,408	61,120	58,889	56,957
Cumulative events							
A1	0	2,101	4,492	6,922	9,242	11,252	13,159
B	0	2,138	4,031	5,943	7,798	9,657	11,589
Survival							
A1	1.00	0.94	0.87	0.81	0.74	0.68	0.63
B	1.00	0.97	0.94	0.92	0.89	0.86	0.83

Table 6: Restricted survival time distribution and comparison for Population A1 and B

Population	Number of individuals	Number of Events	Restricted mean survival time (STD)	Median (95% CI)	Hazard Ratio	95% CI	P-value
A1	35,870	13,159	4.86 (+/-0.01)	NR	**2.508**	[2.446;2.572]	<.0001
B	71,740	11,589	5.49 (+/-0.01)	NR	1.000		.

NR : not reached

Survival of population A1 vs population A2

After matching, for population A1, out of a total of 39,709 individuals, 15,940 events were observed. The calculated restricted mean survival time was 4.72 years (±0.01). The median survival time was not reached, indicating that more than half of the individuals were still alive at the end of the study period, and the 95% confidence interval for the median was not provided.

For population A2, also comprising 39,709 individuals, 13,858 events were observed. The restricted mean survival time was slightly higher at 4.94 years (±0.01). As for population A1, the median survival time was not reached, indicating a similar pattern of survival among individuals in population A2.

Furthermore, when comparing restricted survival time distribution between population A1 and A2, it was found that population A1 had a higher hazard ratio (HR) of 1.206 (95% CI: 1.178 to 1.233) compared to population A2. This difference was statistically significant with a p-value of less than 0.0001, indicating a notable disparity in survival outcomes between the two populations (*Figure 6* and *Table 7*).

Figure 6: Kaplan Meier modeling of survival in population A1 and A2

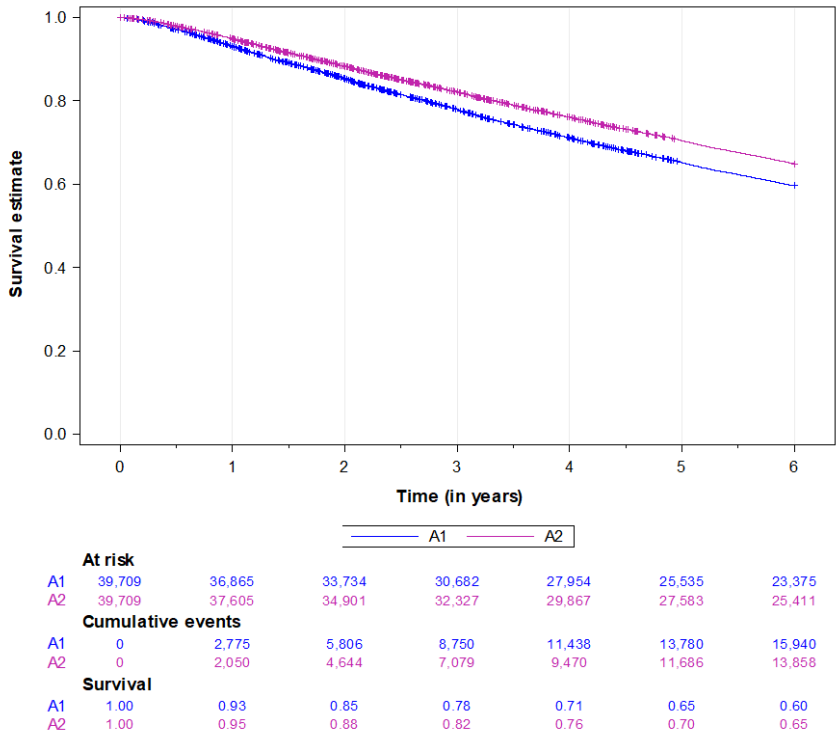


Table 7: Restricted survival time distribution and comparison for population A1 and A2

Population	**Number of individuals**	**Number of Events**	Restricted mean survival time (STD)	Median (95% CI)	**Hazard Ratio**	**95% CI**	**P-value**
A1	39,709	15,940	4.72 (+/-0.01)	NR	**1.206**	[1.178;1.233]	<.0001
A2	39,709	13,858	4.94 (+/-0.01)	NR	1.000		.

NR: not reached

Discussion

This study provides a comprehensive evaluation of mortality and clinical outcomes among patients with COPD receiving triple therapy in France, using robust national-level data from the SNIIRAM database. The findings highlight significant differences in mortality risk, healthcare utilization, and disease burden between patients with uncontrolled COPD (Population A1), those with controlled COPD (Population A2), and the general population (Population B).

The analysis revealed a markedly higher mortality risk among patients in Population A1 compared to both Population B and Population A2. The restricted mean survival time was significantly lower in A1 (4.86 years) than in B (5.49 years), with a hazard ratio (HR) of 2.508, indicating more than double the risk of death. Even when compared to A2, the HR of 1.206 underscores the elevated mortality burden in patients with frequent or severe exacerbations despite triple therapy. These findings emphasize the prognostic significance of exacerbation history and suggest that current treatment strategies may be insufficient for a substantial subset of patients.

Limitations

The SNIIRAM database, being a reimbursement database, records all prescriptions for delivered and reimbursed products, while it did not capture self-medication or consumption of prescribed treatments but not reimbursed. Additionally, medical results such as laboratory tests or medical imaging results were not included in the database.

To identify comorbidities of interest, published algorithms were used when available. However, at the hospital level, only clinical events leading to hospitalization and described in the diagnoses of that hospitalization were identifiable. Therefore, events such as mild or moderate exacerbations that did not result in hospitalization might have been missed.

Furthermore, the date of initial diagnosis of COPD was often unknown unless the severity of the disease required the patient to be declared as having a chronic illness. Therefore, the diagnosis of mild COPD could only be estimated based on specific prescriptions or medical procedures, as defined by algorithms. Moreover, the patient inclusion design corresponded to a given state of the population of interest included in 2015. In particular, the A2 population did not correspond strictly speaking to a non-exacerbating or controlled population, but to a population considered to be controlled within a one-year period.

Conclusion

This comprehensive analysis of COPD patients receiving triple therapy in France, utilizing data from the SNDS database, highlights significant demographic and clinical disparities between patients identified as uncontrolled and controlled during a one-year period and the general population. Patients identified as uncontrolled COPD patients on triple

therapy were predominantly older men and exhibited higher rates of exacerbations, hospitalizations for dyspnea, and respiratory rehabilitation sessions. The survival analysis indicated poorer outcomes for patients identified as uncontrolled COPD patients, who had significantly higher hazard ratios compared to both patients identified as controlled COPD patients and the general population. The hazard function revealed that patients identified as uncontrolled COPD patients had a lower median time to exacerbation or death and experienced subsequent exacerbations more rapidly than patients identified as controlled COPD patients, indicating increased vulnerability over time.

Appendix C. US MarketScan

Title

Chronic Obstructive Pulmonary Disease (COPD) Mortality in the USA from the MarketScan Database

Aim

To evaluate all-cause and COPD-related mortality among patients with uncontrolled COPD in the United States and compare it with general COPD and non-COPD populations using real-world data.

Study Design

Data source
This retrospective study aimed to evaluate mortality rates, patient characteristics, COPD-related factors, and treatment patterns among adult patients uncontrolled COPD. The study utilized the Merative MarketScan® Research Database, a comprehensive US commercial claims database encompassing claims, hospital records, electronic health records (EHR), clinical data, and specialty databases, covering over 245 million unique patients since 1995. For this study, several Merative MarketScan® data sources were retrieved in an extraction: Commercial Claims and Encounters Data (CCAE) database, Medicare Administrative Claims Database, pharmacy claims data, laboratory outpatient data, mortality data and inpatient hospital stay data. The analysis was conducted on an extraction of MarketScan® data including COPD patients and randomly selected non-COPD patients matched on gender and age following the ratio 1:10 from year 2018 to 2022.

Two main databases within Merative MarketScan® were utilised:

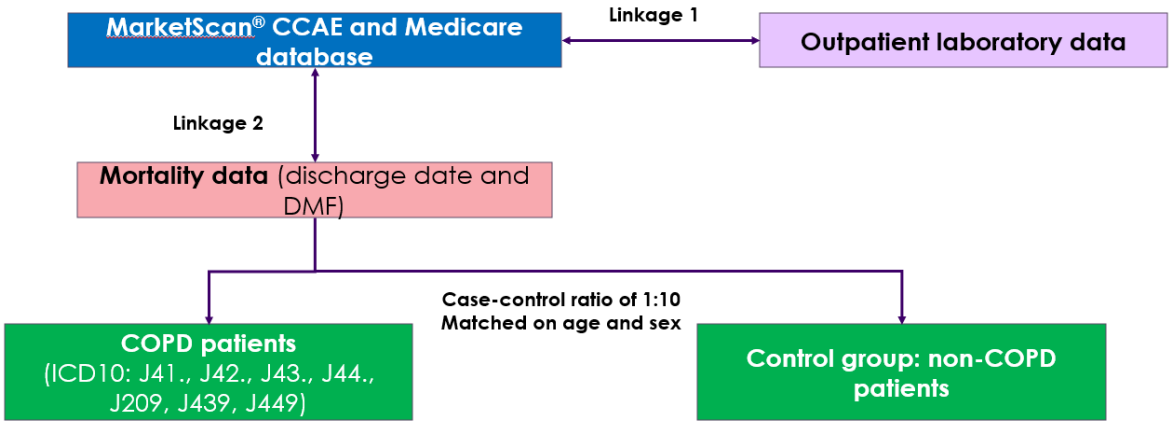
1. **Merative MarketScan® CCAE database:** A longitudinal patient-level database containing demographic information, medical claims files, financial data, and drug information for privately insured individuals in the United States.23 Outpatient laboratory data was linked to the claims data and contain information on various diagnosis tests and procedures performed.
2. **Medicare administrative claims databases**: Provided by the Centers for Medicare and Medicaid Services, these databases cover encounters with the healthcare system and therapeutic interventions for beneficiaries aged ≥65 years and selected individuals with disabilities aged <65 years.24 Outpatient laboratory data was also linked to the Medicare claims data to gather information on various diagnosis tests and procedures performed.

To address the study objectives, mortality data from patient hospital discharge status and the death master file (DMF) was linked to the CCAE and Medicare databases. The DMF is a registry that accumulates records of deceased individuals who were recipients of Social Security benefits. The compilation of death records in the DMF was facilitated

through reports from various entities, including family members, funeral homes, financial institutions, postal services, state governments, and other federal agencies.

The Figure 7 below details the different Merative MarketScan® data linkages as well as the identification of the COPD population and a general population sample of patients without COPD diagnoses.

Figure 7. Data sources



Abbreviations: CCAE: Commercial Claims and Encounters Data; COPD: Chronic obstructive pulmonary disease; ICD: international classification of disease and related health problems.

Study design

Study population
Three populations of interest were defined to generate analyses for the study objectives:

- **Case cohort: uncontrolled COPD population** (main population of interest)
- **Control cohort 1: general COPD population** (including uncontrolled COPD main population)
- **Control cohort 2: Non-COPD population** (sample of general population without COPD diagnoses).

The following inclusion and exclusion criteria were used to define the case (i.e., uncontrolled COPD) and control (i.e., general COPD, Non-COPD) population.

Identification of COPD patients

Inclusion criteria:

- Patients were between **40-80 years old**.
- Patients were with ≥2 separate medical claims with an ICD-10 diagnosis code for COPD during the inclusion period (1st January 2018 and 31st December 2022), and the 2nd COPD claims occurred after the year 2019.
- All selected patients were required to have one-year continuous enrolment in the pre-index (i.e., baseline) period.

Exclusion criteria:

- Patients were with missing key demographic variables (sex, age) in database.
- Patients were with asthma, cystic fibrosis, interstitial lung disease, bronchiectasis, or alpha-1 antitrypsin deficiency in the 12 months prior COPD diagnosis; evidence was based on diagnosis.

Identification of uncontrolled COPD patients

Uncontrolled COPD patients were defined based on COPD exacerbation episodes throughout the entire study period among all the COPD patients.

COPD exacerbation events were classified as moderate or severe exacerbation events based on the following methodology:

- **Moderate exacerbation events** were defined as an outpatient visit with a COPD diagnosis, and a claim for rescue medication within 7 days of the outpatient visit.
- **Severe exacerbation events** were defined by following either the following two criteria:
    - Inpatient hospitalization with a primary COPD (ICD-10: J41.X, J42.X, J43.X, J44.X) diagnosis.
    - Emergency room (ER) visit with a primary COPD diagnosis and a claim for IV corticosteroids within 7 days of inpatient admission code or date of the ER visit.
- The admission date of inpatient hospitalization or date of ER visit was considered as the start date of exacerbation, while the discharge date of inpatient hospitalization or date of ER visit was considered as the end date of exacerbation.

Exacerbation events occurring within 14 days of the end date of another exacerbation event were combined into one single exacerbation episode.

- The start date of the first exacerbation event in an episode was considered as the start date of the exacerbation episode.
- The maximum of the end dates of all exacerbation events in an episode was considered as the end date of an exacerbation episodes.
- The severity of an exacerbation episode was determined by the most sever event during the episode.

COPD patients had ≥2 moderate exacerbation episodes that were < 12 months apart, or had ≥1 severe exacerbation episodes were classified as uncontrolled COPD cohorts.

Identification of non-COPD patients

Merative MarketScan® supplied a control group composed of non-COPD individuals from the general population, drawn from the Merative MarketScan® CCAE and Medicare databases. These controls were matched 10:1 to cases (vs. overall COPD population) on gender and age variables. This matching process was be performed prior to the receipt of data from Merative MarketScan®.

Inclusion criteria (for non-COPD cohort):

- Patients were with no history of COPD as identified by ICD-10 diagnosis code for COPD. Patients were between 40-80 years old.
- All selected patients were required to have one-year continuous enrolment in the pre-index period

Exclusion criteria (for non-COPD cohort)

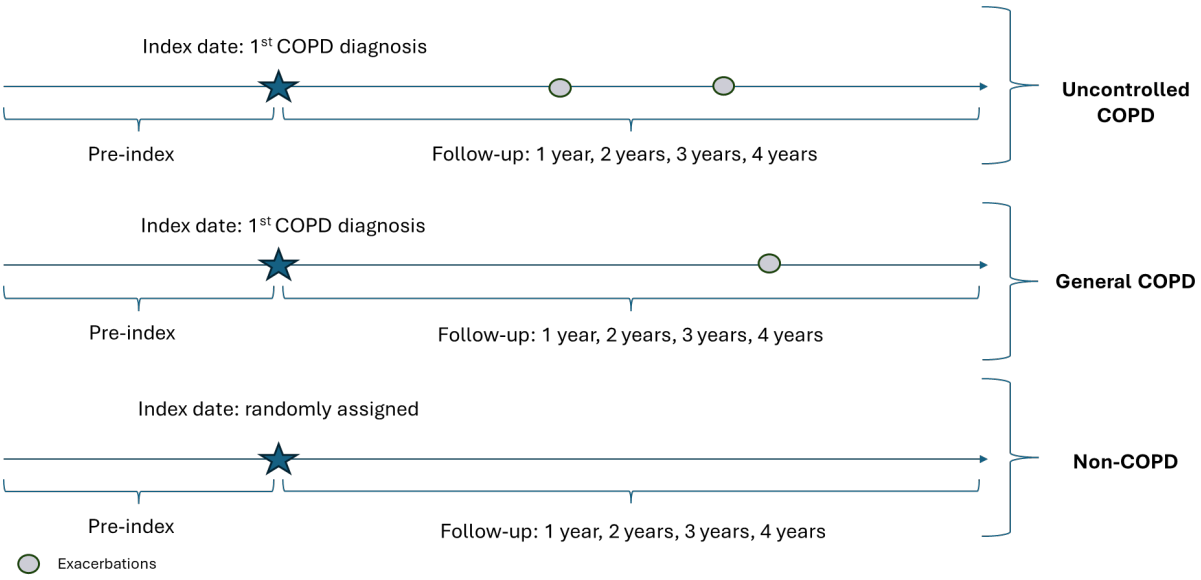
- Patients were with missing key demographic variables (sex, age) in database.
- Patients were with asthma, cystic fibrosis, interstitial lung disease, bronchiectasis, or alpha-1 antitrypsin deficiency.

Study periods of interest

The Merative MarketScan® dataset included observations from January 1st, 2018, up to December 31st, 2022, this included a one-year pre-index period to enable a comprehensive understanding of patient treatment pathways. The inclusion period covered four years from the most recent available data (2019-2022). The analysis on the primary outcome (i.e., all-cause mortality, COPD-related mortality) and secondary outcome (e.g., exacerbation, comorbidity) were conducted during the overall study period and by different years of follow-up (Figure 8).

Index date for COPD patients

Figure 8. Study design overview



Abbreviations: COPD: Chronic obstructive pulmonary disease.

For patients with uncontrolled or general COPD, the index date was defined as the date of the 1st COPD diagnosis, with one-year pre-index (baseline) period. The follow-up period was defined as the period starting from index date (i.e., date of the 1st COPD diagnosis) to the end of follow-up of the patient (death, end of enrolment).

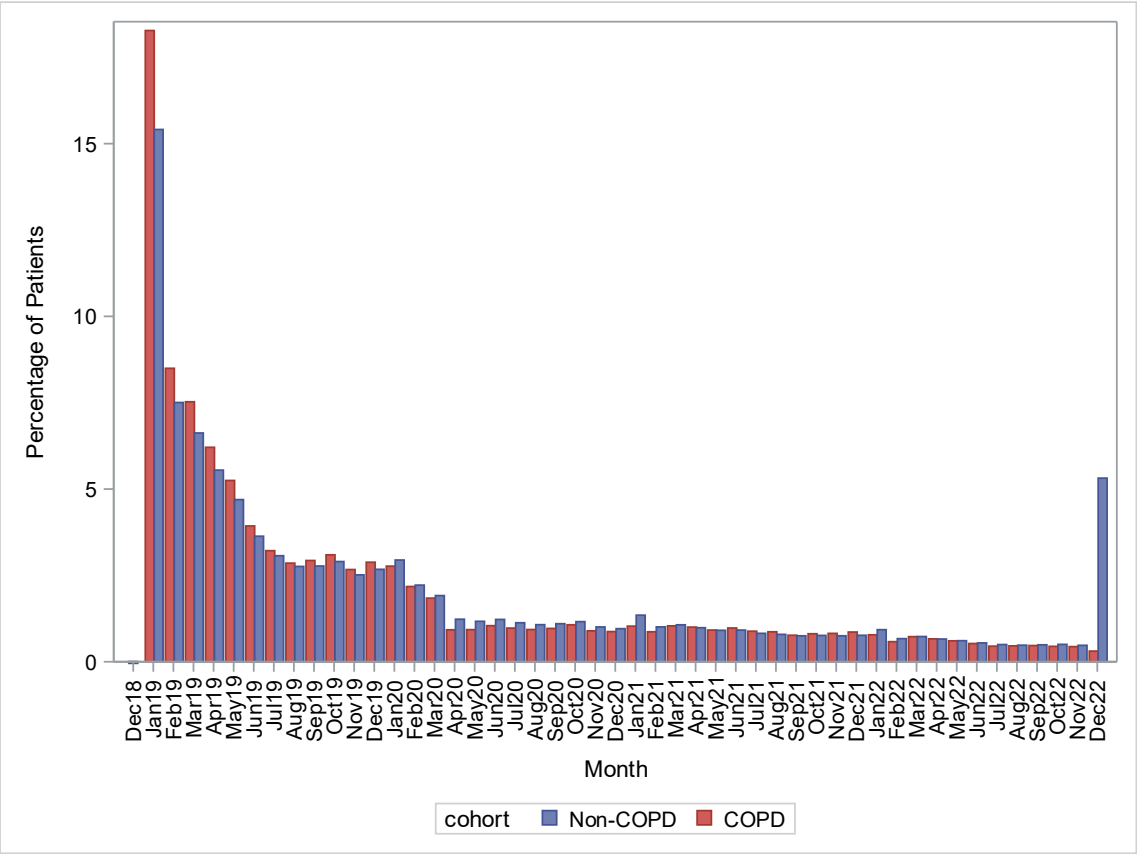
Index date for non-COPD patients

For non-COPD patients, the index date was developed based on previous methodology, randomly assigning index dates to control groups (i.e., non-COPD cohort) in retrospective studies, ensuring the distribution of these proxy dates aligns with that total of the actual index dates of the case (i.e., general COPD) cohort. The method has been applied to other MarketScan® study. The steps of index date imputation are followed:

- **Calculate time difference for case cohort:** for the individuals in the general COPD cohort, the time difference (in months) between a reference date (chosen to be the first date of enrolment) and the 1st COPD diagnosis (index date) was calculated.
- **Definition of strata:** Based on the distribution of the calculated time difference, strata were created to represent the intervals of time between the reference date and index date. Each of the stratum was assigned with a similar percentage of patients from the non-COPD cohort (i.e., if 20% of the COPD cohort had a time difference of 3 months between reference date and first COPD diagnosis, then 20% of the non-COPD cohorts were assigned to have a proxy date at 3 months from the reference date).
- **Random assignment of proxy dates:** a random date within non-COPD patients' assigned strata was chosen as the proxy date.
- **Validation:** frequency distributions of time from the reference date to the index date were compared between the COPD and non-COPD groups to confirm alignment.

The distribution of index dates by month in the non-COPD cohort closely mirrored that of the general COPD cohort across the study period, confirming the success of the imputation strategy (Figure 9). A spike in December 2022 reflected a limitation of the method, where imputed dates exceeding the data cutoff were reassigned to the last available month.

Figure 9. The distribution of imputed index date of non-COPD cohort compared to general COPD cohort.



Abbreviations: COPD: Chronic obstructive pulmonary disease.

Outcomes and analyses of interest

Outcomes of interest including baseline demographics and clinical characteristics, all-cause mortality, COPD-related mortality, COPD exacerbation, comorbidities, treatment patterns and the association between mortality and COPD-related factors were generated.

Description of patients' demographics and clinical characteristics

Patients' demographics and clinical characteristics were described at index date or during the pre-index period for cases (i.e., uncontrolled COPD) and controls (i.e., general COPD, non-COPD).

The demographics included:

- Age
- Sex

- Insurance plan
- Geographical region

Clinical characteristics were evaluated during the pre-index period for all populations for case (i.e., uncontrolled COPD) and control (i.e., general COPD, non-COPD) patients

For the **COPD population only**, the following clinical characteristics were investigated:

- **Exacerbation history** during the baseline period (pre-index). The identification of the severity of exacerbation history followed the same methods that used to identify the uncontrolled COPD cohort.
- **The type of index COPD therapy**:
    - **Monotherapy**: long-acting β2-agonist (LABA), long-acting muscarinic antagonist (LAMA), short acting β2-agonist inhalers (SABA), short acting antimuscarinic inhalers (SAMA)
    - **Double inhalers therapy**: LABA+LAMA, SABA+SAMA.
    - **Triple inhalers therapy**: LABA+LAMA+ICS.

To be notice the short-acting bronchodilators (i.e., SABA, SAMA) were often prescribed as rescue medication to improve symptoms.

Eosinophil levels based on outpatient laboratory data were described at index date. According the GOLD report,[10] blood eosinophil counts were categorized into three specific categories:

- <100 cells/μL
- 100 cells/μL - 300 cells/μL
- ≥ 300 cells/μL

This categorization was based on published evidence of several studies demonstrating a link between eosinophil levels and response to treatments, especially inhaled corticosteroid (ICS), with lower eosinophil levels linked to poor effect of ICS.

Descriptive statistics were calculated for the demographic and clinical characteristics for both case (i.e., uncontrolled COPD) and control (i.e., general COPD and non-COPD patients) cohorts.

- Variables calculated as continuous variable: age (mean, median), CCI (mean), and rate of COPD exacerbation events during pre-index period (mean).

Variables calculated as categorical variables based on the proportion of patients in different categories: age group, sex, insurance plan, geographical region, CCI index level, patients with different comorbidities, patients with exacerbation history, and eosinophil count level.

Primary outcomes: mortality-related outcomes

The primary objective of this study was the analysis of mortality of uncontrolled COPD patients.

The raw mortality rates were expressed as the proportion of individuals who experienced the event within each time of follow up (Figure 8), separately for all-cause and COPD-related deaths. The following algorithm was applied to determine whether the death was linked to COPD and thus determine COPD-related death vs all-cause death:

- For patients who **died during an inpatient stay**, the COPD diagnostic ICD-10 codes listed in the final inpatient claim were used to identify the COPD-related death. If the date of death was linked to the discharge date of the last inpatient claim, the COPD-related death status was classified as missing.
- For patients whose **death was recorded in the DMF**, we assessed inpatient claims that occurred within 90 days prior to the death date for any COPD-related diagnoses. Although no consensus existed in the literature regarding the ideal look-back period, a 90-day window was adopted based on a suggestion from Sanofi.

The following ICD-10 codes were used to determine COPD-related death: bronchitis (J20.9), simple chronic bronchitis (J41), unspecified chronic bronchitis (J42), Macleod syndrome (J43), emphysema (J43.9), and other chronic obstructive pulmonary disease (J44, J44.9). All-cause and COPD related raw mortality rates were calculated during the entire study period and by different years of follow-up (one-year, two-year and three-year, Figure 8) after the index date, stratified by age (i.e., ≤40 years, 45-54 years, 55-64 years, 65-74 years, 75-84 years, 85+ years), sex (i.e., female, male), and exacerbation history (i.e., Yes or No, for patients with COPD only). The analysis on the COPD-related mortality was conducted exclusively for COPD patients (i.e., uncontrolled COPD, general COPD).

To generate evidence on the comparative mortality of uncontrolled COPD versus reference cohorts, the **standardized mortality ratio** (**SMR**) measure was generated. The SMR is the ratio of the number of deaths observed in a study population (i.e., uncontrolled COPD) over a given period to the number that would be expected over the same period if the study population had the same age-specific rates as a defined reference population. The SMR for case (i.e., uncontrolled COPD) cohort was calculated using indirect standardization method, with controls (e.g., general COPD, non-COPD) cohort as the reference standard and its age and sex stratum used to standardize the mortality rates. SMR was calculated for both all-cause mortality and COPD-related mortality, with 95% CI calculated using the Poisson distribution algorithm.

$$SMR = \frac{No.\ observed\ death}{No.\ expected\ death} \qquad 95\%CI\ of\ SMR = 1.96 \times \sqrt{\frac{No.\ observed\ deaths}{No.\ expected\ deaths}}$$

The SMR of all-cause and COPD-related mortality were calculated during the entire study period and by different years of follow-up (one-year, two-year and three-year, Figure 8) after the index date and by age and sex strata. The analysis of the SMR on the COPD-related mortality was conducted exclusively for COPD patients (i.e., uncontrolled COPD, general COPD).

Merative MarketScan® database, a large U.S. claims database containing de-identified healthcare data from employers, health plans, and hospitals.

Summary of analyses was conducted

Table 8 below lists the different analyses of interest were conducted across case (i.e., uncontrolled COPD) and controls (i.e., general COPD, non-COPD) cohorts.

Table 8. Summary of conducted analyses

	Study population: CCAE-Medicare-Mortality-Outpatient laboratory		
	Uncontrolled COPD (case)	Non-COPD (control)	General COPD (control)
Descriptive statistics on patients' demographics and clinical characteristics at index or pre-index			
Descriptive statistics on patients' demographics (age, sex, insurance plan covered) and global clinical characteristics (CCI, comorbidities)	✓	✓	✓
Descriptive statistics on COPD patients for exacerbation history and type of index COPD therapy	✓		✓
Descriptive statistics on COPD patients for eosinophil levels	✓		✓
Primary outcomes			
Mortality and exacerbation rates analysis during follow-up			
Raw all-cause mortality rates stratified by age, sex, exacerbation history	✓	✓†	✓
Raw COPD-related mortality stratified by age, sex and exacerbation history	✓		✓
SMR on all-cause mortality stratified by age-sex stratum	✓	Ref pop.	Ref pop.
SMR on COPD-related mortality stratified by age-sex stratum	✓		Ref pop

Note: †analysis was not stratified by exacerbation history.
Abbreviations: CCAE: Commercial Claims and Encounters Data; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; ref pop: reference population.

Results

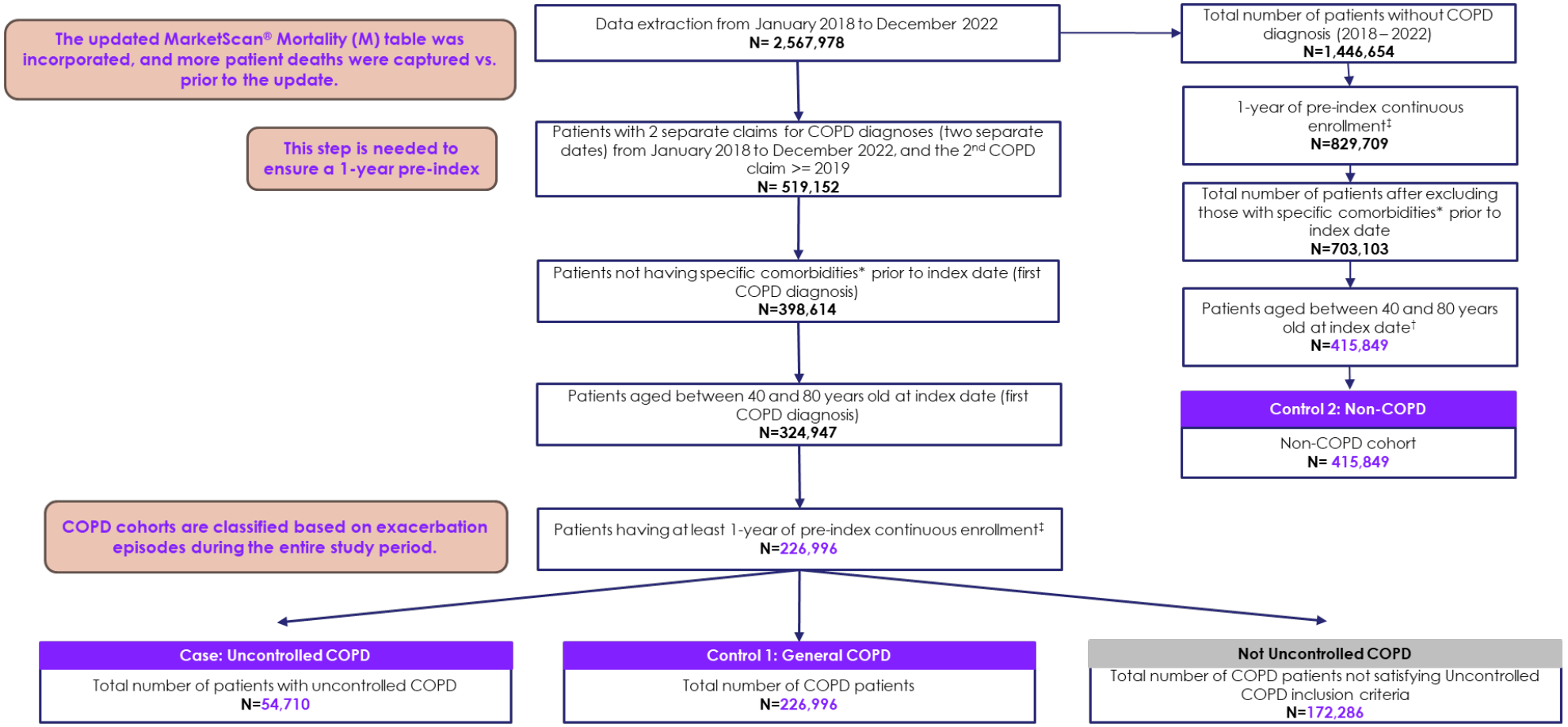
Population identification and patients' characteristics

Patient selection for the case and control cohorts is illustrated in Figure 10, based on the inclusion and exclusion criteria outlined above. A total of 226,996 patients aged 40-80 years old with COPD diagnoses who had ≥2 claims during enrolment, no prior comorbidities, and continuous enrolment were classified as general COPD cohort. In general COPD cohort, 54,710 patients experienced eligible COPD exacerbation episodes during the entire study period, and were classified as case (i.e., uncontrolled COPD) cohort. In addition, 415,849 non-COPD patients were identified for comparison. The Figure 8 illustrates the population selection process according to the cohort.

Descriptive analysis of baseline characteristics were conducted across the different cohorts (Table 9, Table *10*). Sociodemographic variables (i.e., age, insurance plan types, and geographical region) were in general balanced between the uncontrolled COPD cohort and general COPD cohort. In addition, the CCI score (2.26 vs 2.02), COPD exacerbation history (2.53 vs 2.21), and MACE (23.20% vs 20.84%) during the pre-index period were similar between the two cohort (Table 9, Table *10*). A slightly higher proportion of patients in the uncontrolled COPD cohort had CCI score ≥2 (48.23% vs 43.02%), along with a higher prevalence of most comorbidities, compared to general COPD cohort (Table *10*). Notably, higher proportion of patients in the uncontrolled COPD cohort were with exacerbation history (i.e., 41.94%) compared to general COPD cohort (13.05%).

Demographic variables were in general balanced between uncontrolled COPD and non-COPD cohort, except patients in the uncontrolled COPD were older demonstrated as higher mean age (64 vs 55) and higher proportion of patients were >65 years old (42.48% vs 12.15%). Patients in the uncontrolled COPD cohort had more comorbidities during pre-index period, demonstrated as higher CCI score (2.26 vs 0.94), higher proportion of patients with CCI score ≥2 (48.32% vs 19.60%), higher MACE event (23.20% vs 6.82%), and along with higher prevalence of all comorbidities, compared to non-COPD cohort.

Figure 10. Patient selection flow for case and control cohorts



Note: *chronic asthma, cystic fibrosis, interstitial lung disease, bronchiectasis, or alpha-1 antitrypsin deficiency; † as index dates for the non-COPD cohort where imputed, the claim closest to the index date was used to determine the age; ‡ Death date is considered as the maximum follow up when applicable. **Abbreviations**: CCAE: Commercial Claims and Encounters; COPD: chronic obstructive pulmonary disease; N: number

Table 9. Baseline characteristics on socio-demographic variables

Variables	Cohorts		
	Case cohort	Control cohorts	
	Uncontrolled COPD (N = 54,710)	General COPD (N = 226,996)*	Non-COPD (N =415,849)
Age continuous			
Mean (SD)	**63.91 (9.66)**	63.01 (9.64)	**55.47 (9.34)**
Median (Q1, Q3)	**63.00 (57.00, 72.00)**	62.00 (57.00, 71.00)	**55.00 (48.00, 61.00)**
Age categories – N (%)			
≤45 years	**1,963 (3.59)**	9,526 (4.20)	**68,956 (16.58)**
45-54 years	**8,510 (15.55)**	38,948 (17.16)	**143,228 (34.44)**
55-64 years	21,001 (38.39)	93,140 (41.03)	153,117 (36.82)
65-74 years	**15,125 (27.65)**	56,157 (24.74)	**35,906 (8.63)**
75+ years	**8,111 (14.83)**	29,225 (12.87)	**14,642 (3.52)**
Sex – N (%)			
Female	30,049 (54.92)	115,439 (50.86)	237,709 (57.16)
Male	24,661 (45.08)	111,557 (49.14)	178,140 (42.84)
Insurance plan covered – N (%)			
Basic/Major Medical	14 (0.03)	91 (0.04)	134 (0.03)
Comprehensive	**9,921 (18.13)**	34,173 (15.05)	**23,206 (5.58)**
EPO	432 (0.79)	1,764 (0.78)	3,782 (0.91)
HMO	6,717 (12.28)	30,759 (13.55)	64,255 (15.45)
POS	1,696 (3.10)	9,136 (4.02)	25,947 (6.24)
PPO	29,045 (53.09)	120,005 (52.87)	204,588 (49.20)
POS with Capitation	428 (0.78)	2,383 (1.05)	4,566 (1.10)
CDHP	3,984 (7.28)	16,927 (7.46)	49,422 (11.88)
HDHP	2,127 (3.89)	10,084 (4.44)	35,555 (8.55)
Unknown	346 (0.63)	1,674 (0.74)	4,394 (1.06)
Geographical region – N (%)			
Northeast	5,460 (9.98)	27,492 (12.11)	48,049 (11.55)
North Central	**23,648 (43.22)**	90,699 (39.96)	**113,182 (27.22)**
South	22,730 (41.55)	94,291(41.54)	198,841 (47.82)
West	**2,828 (5.17)**	14,241(6.27)	**54,972 (13.22)**
Unknown	44 (0.08)	273 (0.12)	805 (0.19)

Note: *General COPD includes uncontrolled COPD population; variables that demonstrate differences between the case and control cohorts are highlighted in **bold.**
Abbreviation: COPD: chronic obstructive pulmonary disease; EPO: exclusive provider organization; HDHP: high-deductible health plan; HMO: health maintenance organization; N: number; POS: point-of-service; PPO: preferred provider organization; Q1: first quantile; Q3: third quantile; SD: standard deviation

Table 10. Baseline characteristics on clinical variables

Variables	*Cohorts*		
	Case cohort	**Control cohorts**	
	Uncontrolled COPD (N = 54,701)	**General COPD (N = 226,996)***	**Non-COPD (N = 415,848)**
Charlson Comorbidity Index (CCI) – continuous			
Mean (SD)	**2.26 (2.43)**	2.02 (2.44)	**0.94 (1.57)**
Charlson Comorbidity Index (CCI) – N (%)			
0	**12,005 (21.94)**	70,458 (31.04)	**223,937 (53.85)**
1	**16,270 (29.74)**	58,894 (25.94)	**110,417 (26.55)**
≥ 2	**26,435 (48.32)**	97,644 (43.02)	**81,495 (19.60)**
Comorbidity Counts – N (%)			
Cardiovascular Disease	**19,120 (34.95)**	73,040 (32.18)	**52,620 (12.65)**
Hypertension	**34,703 (63.43)**	138,934 (61.21)	**173,164 (41.64)**
Diabetes	**14,290 (26.12)**	59,215 (26.09)	**71,560 (17.21)**
Depression	**10,817 (19.77)**	40,233 (17.72)	**51,111 (12.29)**
Anxiety	**12,562 (22.96)**	45,167 (19.90)	**63,912 (15.37)**
Osteoporosis	**2,951 (5.39)**	10,763 (4.74)	**9,553 (2.30)**
Pneumonia	**6,741 (12.32)**	**18,399 (8.11)**	**9,322 (2.24)**
MACE History – N (%)			
≥ 1 MACE	**12,691 (23.20)**	47,297 (20.84)	**28,348 (6.82)**
With COPD Exacerbation History – N (%)			
Yes	**22,944 (41.94)**	**29,635 (13.06)**	NA
Rate of COPD exacerbation events during pre-index period among patients with COPD exacerbation history - Continuous			
Mean (SD)	2.53 (2.73)	2.21 (2.48)	NA
Eosinophil count reported – N (%)			
	676 (1.24)	3,365 (1.48)	NA
Eosinophil count level among the reported – N (%)			
Low (<100 cells/µL)	594 (87.87%)	2,833 (84.19%)	NA
Median (100 – 300 cells/µL)	58 (8.58%)	413 (12.27%)	
High (≥ 300 cells/µL)	24 (3.55%)	119 (3.54%)	

Note: *General COPD includes uncontrolled COPD population; variables that demonstrate differences between the case and control cohorts are highlighted in **bold.**
Abbreviation: CCI: Charlson Comorbidity Index; COPD: chronic obstructive pulmonary disease; MACE: major adverse cardiac events; N: number; SD: standard deviation

Primary outcome - Mortality analyses

The primary outcome of this study was the reporting and comparison of mortality rates in patients with uncontrolled COPD versus COPD patients in general (including uncontrolled and controlled) as well as versus non-COPD patients.

All-cause and COPD-related mortality were analysed, using the entire follow-up (4 years) period, and by specific length of follow-up (1, 2 and 3 years). Results are reported in the following sections.

All-cause mortality

Raw all-cause mortality rates

Patients in the **uncontrolled COPD** cohort had a **higher all-cause mortality rate** (11.82%) during the overall study period (2019-2022) compared to general COPD cohort (8.82%) and non-COPD cohort (1.51%). The differences in mortality rates were more pronounced among the older age group. In addition, patients in the uncontrolled COPD cohort consistently exhibited higher mortality rates compared to the general COPD cohort and non-COPD cohort regardless of their sex. Notably, patients with a history of exacerbation had similar mortality risk in both the uncontrolled cohort (16.57%) and general COPD cohort (15.43%, Table 11).

Table 11. Raw all-cause mortality during the entire study period

Variables	All-cause mortality rates (2019-2022)					
	Uncontrolled COPD		General COPD		Non-COPD	
	N	Mortality events (%)	N	Mortality events (%)	N	Mortality events (%)
Age categories – N (%)						
≤45 years	1,963	7 (0.36)	9,526	56 (0.59)	68,956	157 (0.23)
45-54 years	8,510	103 (1.21)	38,948	511 (1.31)	143,228	632 (0.44)
55-64 years	21,001	**983 (4.68)**	93,140	3,384 (3.63)	153,117	**1,559 (1.02)**
65-74 years	15,125	**3,031 (20.04)**	56,157	**8,804 (15.68)**	35,906	**2,183 (6.08)**
75+ years	8,111	**2,341 (28.86)**	29,225	**7,255 (24.82)**	14,642	**1,757 (12.00)**
Sex – N (%)						
Female	30,049	**2,978 (9.91)**	115,439	8,323 (7.21)	237,709	**2,583 (1.09)**
Male	24,661	**3,487 (14.14)**	111,557	**11,687 (10.48)**	178,140	**3,705 (2.08)**
COPD exacerbation history – N (%)						
Yes	22,944	3,802 (16.57)	29,635	4,574 (15.43)	0	NA
No	31,766	2,663 (8.38)	197,361	15,436 (7.82)	415,849	6,288 (1.51)
Total	**54,710**	**6,465 (11.82)**	**226,996**	**20,010 (8.82)**	**415,849**	**6,288 (1.51)**

Note: Mortality rates that demonstrate differences between the case and control cohorts are highlighted in **brown. Abbreviation**: COPD: chronic obstructive pulmonary disease; N: number

Analyses of all-cause mortality were conducted by different years of follow-up (i.e., one-year, two-year, and three-year) after the index date. All-cause mortality rate in the uncontrolled COPD cohort was slightly lower than in general COPD cohort during one-year follow-up (2.83% vs 3.28%), while higher mortality rate in the uncontrolled COPD

cohort compared to general COPD cohort during the two-year (6.02% vs 5.66%) and three-year follow-up (9.42% vs 7.72%). In addition, the all-cause mortality rates in the uncontrolled COPD cohort were consistently higher than the non-COPD cohort across different follow-up periods. Furthermore, patients with exacerbation history demonstrated similar mortality rates in uncontrolled COPD cohort compared to general COPD cohort which was consistent across different years of follow-up (Table 12, Table 13 and Table 14).

Table 12. Raw all-cause mortality during one-year follow-up after the index date

Variables	All-cause mortality rates (One-year follow-up)					
	Uncontrolled COPD		General COPD		Non-COPD	
	N	Mortality events (%)†	N	Mortality events (%)†	N	Mortality events (%)†
Age categories – N (%)						
≤45 years	1,963	3 (0.15)	9,526	28 (0.29)	68,956	44 (0.06)
45-54 years	8,510	33 (0.39)	38,948	207 (0.53)	143,228	205 (0.14)
55-64 years	21,001	**250 (1.19)**	93,140	1,349 (1.45)	153,117	**480 (0.31)**
65-74 years	15,125	**706 (4.67)**	56,157	3,150 (5.61)	35,906	**702 (1.96)**
75+ years	8,111	**558 (6.88)**	29,225	**2,707 (9.26)**	14,642	**561 (3.83)**
Sex – N (%)						
Female	30,049	**709 (2.36)**	115,439	3,051 (2.64)	237,709	**819 (0.34)**
Male	24,661	**841 (3.41)**	111,557	4,390 (3.94)	178,140	**1,173 (0.66)**
COPD exacerbation history – N (%)						
Yes	22,944	1,059 (4.62)	29,635	1,436 (4.85)	0	NA
No	31,766	491 (1.55)	197,361	6,005 (3.04)	415,849	1,992 (0.48)
Total	**54,710 (70.85%)**	**1,550 (2.83)**	**226,996**	7,441 (3.28)	**415,849**	**1,992 (0.48)**

Note: Proportion of patients who experienced uncontrolled COPD during the follow-up year were highlighted in **blue**; mortality rates that demonstrate differences between the case and control cohorts are highlighted in **brown. Abbreviation**: COPD: chronic obstructive pulmonary disease; N: number

Table 13. Raw all-cause mortality during two-year follow-up after the index date

Variables	All-cause mortality rates (Two-year follow-up)					
	Uncontrolled COPD		General COPD		Non-COPD	
	N	Mortality events (%)†	N	Mortality events (%)†	N	Mortality events (%)†
Age categories – N (%)						
≤45 years	1,963	5 (0.25)	9,526	47 (0.49)	68,956	98 (0.14)
45-54 years	8,510	51 (0.60)	38,948	339 (0.87)	143,228	385 (0.27)
55-64 years	21,001	**503 (2.40)**	93,140	2,214 (2.38)	153,117	**968 (0.63)**
65-74 years	15,125	**1,508 (9.97)**	56,157	5,538 (9.86)	35,906	**1,369 (3.81)**
75+ years	8,111	**1,227 (15.13)**	29,225	4,717 (16.14)	14,642	**1,106 (7.55)**
Sex – N (%)						
Female	30,049	**1,467 (4.88)**	115,439	5,234 (4.53)	237,709	**1,605 (0.68)**
Male	24,661	**1,827 (7.41)**	111,557	7,621 (6.83)	178,140	**2,321 (1.30)**
COPD exacerbation history – N (%)						
Yes	22,944	2,064 (9.00)	29,635	2,613 (8.82)	0	NA
No	31,766	1,230 (3.87)	197,361	10,242 (5.19)	415,849	3926 (0.94)
Total	**54,710 (85.22%)**	**3,294 (6.02)**	**226,996**	12,885 (5.66)	**415,849**	**3,926 (0.94)**

Note: Proportion of patients who experienced uncontrolled COPD during the follow-up year were highlighted in **blue**; mortality rates that demonstrate differences between the case and control cohorts are highlighted in **brown. Abbreviation**: COPD: chronic obstructive pulmonary disease; N: number

Table 14. Raw all-cause mortality during three-year follow-up after the index date

Variables	All-cause mortality rates (Three-year follow-up)					
	Uncontrolled COPD		General COPD		Non-COPD	
	N	Mortality events (%) †	N	Mortality events (%) †	N	Mortality events (%) †
Age categories – N (%)						
≤45 years	1,963	7 (0.36)	9,526	56 (0.59)	68,956	137 (0.20)
45-54 years	8,510	85 (1.00)	38,948	461 (1.18)	143,228	581 (0.41)
55-64 years	21,001	**777 (3.70)**	93,140	2,983 (3.20)	153,117	**1377 (0.90)**
65-74 years	15,125	**2,386 (15.78)**	56,157	**7,631 (13.59)**	35,906	**1906 (5.31)**
75+ years	8,111	**1,896 (23.38)**	29,225	**6,400 (21.90)**	14,642	**1523 (10.40)**
Sex – N (%)						
Female	30,049	**2,347 (7.81)**	115,439	7,245 (6.28)	237,709	**2,293 (0.96)**
Male	24,661	**2,804 (11.37)**	111,557	**10,286 (9.22)**	178,140	**3,231 (1.81)**
COPD exacerbation history – N (%)						
Yes	22,944	3,036 (13.23)	29,635	3,729 (12.58)	0	NA
No	31,766	2,115 (6.66)	197,361	13,802 (6.99)	415,849	5524 (1.33)
Total	**54,710 (95.27%)**	**5,151 (9.42)**	**226,996**	**17,531 (7.72)**	**415,849**	**5,524 (1.33)**

Note: Proportion of patients who experienced uncontrolled COPD during the follow-up year were highlighted in **blue**; mortality rates that demonstrate differences between the case and control cohorts are highlighted in **brown. Abbreviation**: COPD: chronic obstructive pulmonary disease; N: number

Limitations Impacting Mortality Interpretation

Several limitations should be considered when interpreting the mortality outcomes:

- Lack of smoking status and eosinophil data: These are key prognostic factors in COPD but were not available for most patients due to data linkage limitations.
- No matching across cohorts: Although standardized rates were used to mitigate bias, the absence of matching may introduce residual confounding.
- Claims-based definitions: The identification of uncontrolled COPD relied on proxy definitions based on exacerbation frequency, which may not fully capture clinical severity.
- Index date limitations: The first recorded COPD diagnosis may not reflect the true onset of disease, especially for patients diagnosed before 2018.
- Population representativeness: The MarketScan® database primarily includes individuals with employer-sponsored insurance, potentially underrepresenting older adults, lower-income groups, and those on public insurance programs.

Implications for Practice and Research

This study reinforces the critical importance of identifying and managing patients with uncontrolled COPD early in their disease course. The elevated mortality risk in this group calls for targeted interventions, including optimized pharmacotherapy, comorbidity

management, and potentially the use of biomarkers (e.g., eosinophils) to guide treatment. Future research should aim to incorporate clinical data such as smoking history and biomarker profiles to refine risk stratification and personalize care.

Appendix D. Calculation of the overall mortality rate from Whittaker 2024.

The overall mortality rate in Whittaker 2024 is not reported so we have attempted to calculate this from the aviable data. Taking a simplistic approach and weighting the proportion of patients with 230,191 patients with rate of 47.5 / 1000 patient years) and without exacerbations (109,456 patients with rate of 64.2 / 1000 patient years) by patient number provides an estimate of 52.88 per 1000 patient years [((230191 *47.5) + (109456 * 64.2)) / 339647 = 52.88]

However, this relies on a fairly strong and untestable assumption (given the data available in the Whittaker paper): **that person years are identical between the subgroups**. This is because the Crude mortality rates are expressed per 1000-person years, so weighting by the proportion of patients in a subgroup and re-combining is implicitly assuming that the subgroups have equal person years on average. This assumption may not hold as patients with exacerbations may have a higher mortality rate and thus less follow-up on average than patients without exacerbations.

The ideal approach of weighting by person years in each category is not possible with the given data would likely have down weighted the more severe subgroups (due to having presumably fewer person years), reducing the estimated mortality. Hence, there's a plausible reason that the simplistic approach to re-weighting may be overestimating the mortality.

We have attempted to validate this in the following way with a simple demonstration using some hypothetical average follow-ups, which, alongside the crude mortality rates and patient numbers from Whittaker et al., have been used to calculate total person years and deaths. Using these values, we have then estimated the overall population crude mortality rate using each weighing approach:

Subgroup	n	Average follow-up (yrs)	Total person years	Deaths	CMR (/1000 PY)
No exacerbations	230191	10	2301910	109340.725	47.5
Any exacerbations	109456	8.5	930376	59730.1392	64.2
Total	339647		3232286	169070.8642	
Overall CMR (weighted by n in subgroup)	52.88180876				
Overall CMR (weighted by person-years)	52.30690112				

Using those numbers, the person-years approach produces a slightly smaller crude mortality rate (~52.31) than your current approach.

However using additional values from Whittaker 2024 it may be possible to back-calculate the average follow-up years in each subgroup and then re-calculate the overall crude morality rate, but weighted by the follow-up years per subgroup

1. The paper states that there were 97882 deaths in the overall population, meaning that **28.8% of the population died**. We can use this value to validate the CMR per 1000 person years

2. The paper states that the **mean follow-up in the overall population was 5.5 years**.

3. We know the proportion of patients in the no exacerbations subgroup is **~0.678 (n=230191)** and **~0.322 (n=109456)** in the any exacerbations subgroup.

4. We know the crude mortality rate per 1000 person years of the no exacerbations subgroup is **47.5** and **64.2** for the any exacerbations subgroup.

Using this information, alongside the data on the proportion of patients in each subgroup, we can construct a system of linear equations, in which we solve for the average years of follow-up in the no exacerbations (x) and any exacerbations (y) subgroups. This simplifies to the following:

1. $0.677736002x + 0.322263998y = 5.5$

2. $(230191*47.5/1000*x)+ (109456*64.2/1000*y) = 10934.0725x + 7027.0752y = 97882$

Equation (1) captures the fact that the average of the subgroups' mean follow-ups must be 5.5 years (where the coefficients are the proportion of the overall population in each subgroup), and Equation (2) captures the fact that the deaths across the subgroups must align with the overall deaths reported (where the coefficients are the deaths per year of follow-up by subgroup, calculated by multiplying the subgroup n by the crude mortality rate / 1000).

Solving for the above gives the following values of x and y:

x = 5.73524

y = 5.00528

This reveals that the mean follow-up in the no exacerbations subgroup is approximately 5.74 years and 5.00 years in the any exacerbations subgroup. Using these values in the calculations used in the example above:

Subgroup	n	Average follow-up (yrs)	Total person years	Deaths	Deaths per years of follow-up	CMR (/1000 PY)
No exacerbations	230191	5.74	1320200.631	62709.52996	10934.0725	47.5
Any exacerbations	109456	5.01	547857.9277	35172.47896	7027.0752	64.2
Total	339647	5.50	1868058.559	97882.00892		
Overall CMR per 1000 person years (weighted by n in subgroup)	52.88180876					
Overall CMR per 1000 person years (weighted by person-years)	52.3977198					
Overall mortality	28.81874679					

We now get an estimated crude mortality rate per 1000 person years of **~52.398**, which is only marginally lower than the original crude estimate and now aligns with the overall mortality reported in the paper (28.8%) to 5 decimal places.

These solutions are approximate in the sense that they don't fully account for rounding (e.g., what the exact value of crude mortality per 1000 years was, since it's reported to 1 decimal place only). However, they should are sufficiently accurate to illustrate the point and provide a robust demonstration about how follow-up in the study may influence the estimates.

Appendix E. Calculation of the moderate and severe exacerbation rates in Whittaker 2024.

The moderate and severe exacerbation rates (AERs) at baseline are not available Whittaker 2024 and so we have attempted to estimate them in the following way.

Categories	Figure	Notes / Source
Total COPD patients	339647	Whittaker 2024
Mean follow-up time	5.5	Whittaker 2024
Total follow-up time	1868058.5	C3 x C4
Exacerbations Severity		
Total patients with exacerbations	109,456	Whittaker 2024 (Table 1)
Patients with only moderate exacerbations	94,853	Whittaker 2024 (Table 1)
Patients with ≥1 severe exacerbation	14,603	Whittaker 2024 (Table 1)
Exacerbation frequency distribution		
1–2 exacerbations	69,695	Whittaker 2024 (Table 1)
>2 exacerbations	39,761	Whittaker 2024 (Table 1)
Estimate Total Moderate Exacerbations		
1–2 exacerbations	104542.5	1–2 exacerbations = 69,695 Therefore, assuming half had 1 exacerbation and half had 2
>2 exacerbations	119283	assume an average of 3 moderate exacerbations per patient
Total estimated moderate exacerbations	223825.5	C14 + C15
Moderate AER	0.12	C16 / C5
Estimate Total Severe Exacerbations		
Patients with ≥1 severe exacerbation	14,603	Whittaker 2024 (Table 1)
Total estimated severe exacerbations	29206	C19 x 2
Severe AER	0.02	C20/C5

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Association of Respiratory Nurses

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	As a nursing organisation we are concerned that the recommendation not to approve dupilumab will negatively impact people who are likely to benefit from this treatment. Acute exacerbations of COPD (AECOPD) are costly for the NHS and society, but the impact on the patient cannot be

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	restricted to financial impact. People who suffer from AECOPD are at risk of future exacerbations with an increasing level of impact holistically.
2	People who suffer from AECOPD are at increased risk of cardiovascular events and there is potential to reduce this risk if the risk of further AECOPD is decreased.
3	The financial impact of dupilumab in terms of DALYs for AECOPD is set at a different level from that used for asthma. The implication is that the lives of people with COPD is worth less than those of people living with asthma. This has an impact with respect to equity of access to treatment when comparing the two conditions.
4	The selectivity of the data NICE has used to underpin its economic model is an issue as it appears to inaccurately predict the clinical benefits of dupilumab for this population. The focus on mortality data is misplaced..
5	The assumption that the benefits of dupilumab may not last do not align with the data.
6	Roflumilast is rarely used in our experience due to the high level of side effects so cannot be included as a realistic option to treat.

Insert extra rows as needed

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- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Thoracic Society

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
General	This is the first new, effective treatment for 20 years in COPD. For a disease that is the third largest cause of mortality and fourth largest cause of disability adjusted life years in the UK this is

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	a travesty. Yet, we now have the first new treatment that is effective and yet the bar to cross seems higher than other conditions. It appears to suggest that there is not enough funding to warrant use. This is disappointing to clinicians as we see so many people who would benefit from marginal gains in their health (reducing exacerbations or improving QOL). We all see many admitted regularly with severe disease and certainly a review of the literature is that this would reduce admissions by around 33% (so better than a statin, ACE inhibitor, clopidogrel and far better than angioplasty / CABG). There was optimism that if this was replicated in all patients - and in most conditions earlier intervention with effective treatments (eg aspirin / statin / ACE) has equivalent and long term beneficial outcomes. Our patients often disadvantaged through social inequities will be disappointed and we are that our patients will not be given the opportunity to benefit. Beyond this, the use of dupilumab would reduce exposures to repeated courses of oral corticosteroids. Overall as a community we are concerned that patients with COPD, who are typically older and have co-morbidities are put at a disadvantage compared to other populations.
Page 4	Impact of dupilumab on the rate of severe exacerbation and mortality: why is mortality the outcome chosen for this disease but not any others. They specifically want to be told if they are disadavantaging protected groups. Patients with COPD typically come from the most socio-economically deprived areas of the country (it is effectively a disease of the poor). Denying effective treatment to this population seems morally wrong. There seems to be a general opinion that they done it to themselves by smoking, but we don't consider this for heart disease (where smoking is one of the strongest risk factors) or diabetes/obesity, which are equally linked to lifestyle. By looking at the impact of something that was not the primary outcome of the trials, then by definition, the committee are disadvantaging those who are disabled with COPD. Add to this The ICER set for COPD is <20K, whilst in asthma and other conditions it is 30k. So, the arguments should be 1. in other airway diseases (asthma) the primary outcome was the one for which impact was funded (ie reducing exacerbations). Added to this that the ICER was greater. COPD patients are greatly disabled, and more so than asthma patients. So, here the committee are at disadvantaging people with a disability and actively making the goalposts harder to attain. 2. If severe exacerbations and mortality is the outcome, for which they will entertain impact/cost-effectiveness, then they have to be able to allow assumptions into the model. 1 person dies with COPD every 20 mins (ALUK data). 1 person is admitted with COPD exacerbation every 3 minutes (NICE data) and 1 person has an exacerbation every 20 seconds (PCRS data). By reducing that impacts on the PCRS data, you will impact the NICE data and then impact the ALUK data. 3. I would then address that each exacerbation (moderate) leads to risk of severe exacerbation and death (Donaldson Chest 2010; Soler; NCAP). I would probably put all the different evidence that they have ignored (as they state anything they have missed out). Hospitalisation for an exacerbation of COPD is the second leading cause of emergency admissions to hospital for a medical reasons (more than 120,000 admissions per year in England). These typically occur at the busiest times (Winter).

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Page 4	How long any benefits of dupilumab last: This is an odd query - the duration of a drug lasting, is the duration by which it is given for. Dupi data showed that it improves lung function rapidly and persists greater than that of being on placebo. The duration of benefit is quick, and lasts for as long as the drug is administered. This is akin to havin any other biologic. It isnt any different with this disease. In terms of long term effect on lung function, the accepted wisdom is that once someone gives up smoking then lung function loss is the same as the general population (i.e. a product of ageing). This would stand that for every year someone is on a product that stabilises lung function is a year of decline saved. The idea of accelerated lung loss after stopping just seems wrong.
Page 5 3.1	Add exacerbations to end of first sentence. 4 grades: we do not classify obstruction on this premise alone anymore. Certainly treatment is not given based on this premise. This is outdated and committee should be told this.
Page 6 3.2	Azithromycin: add that there is concern regarding - side effects - antimicrobial resistance - antibiotic stewardship - raising health inequality as only given to former smokers (so the 30% who smoke don't get this as it doesn't work; also its about 60% current smokers in the north, thereby raising health inequality) There is no long term data beyond 12 months to support the use of azithromycin, yet we use it both as there is clinical experience but also lack of an alternative. We are likely giving a lot of people prolonged exposure to antibiotics without known effiacacy.
Page 7 3.2	Trial outcomes: there would have been fewer exacerbations and fewer severe events. This is clear as COPD hospitalisations all went down. So impact of drug is likely to wither be the same or even greater than in the trials in real life,
Page 12 3.6	Clinically meaningful improvements in clinical practice: this is an error. ANY improvement in FEV in a disease with not-reversible lung function (as per definition at the intro of COPD) is a clinical improvement. The MCID for 100ml is for inhaled therapies; it has never been viewed in context of inhaled therapies on top with biologics. Change in exacerbation rate: Incorrect: Plenty of evidence that states <20% reduction of exacerbations is plenty. Whilst there isn't an MCID - there doesn't need to be. There is a clinical consensus (refs below). Also, was there an MCID for asthma biologics and exacerbations? DOI: 10.3109/15412555.2012.733463 The concept of an MCID is difficult to apply to an individual here. Exacerbations follow patterns and clusters so preventing one is likely to go on to prevent multiple. The trial data do not cover many patients of super-exacerbators, but there seems to be better effiacacy here.

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Page 17 3.10	This will be helped by the MATINEE study (Mepo in COPD, to be published on the 1st of May) which followed people up for 104 weeks - one due to events and power - as COVID impacted exacerbation event rate. The longer a patient is on it, the better the reduction on exacerbations All cumulative exacerbation figures continue to show separation till end of trial, so this would suggest ongoing efficacy and effectiveness.
Page 23 3.15	Why is the ICER /cost per QALY different from asthma?
Page 26 3.18	Add disability to protected characteristics.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Taskforce for Lung Health and Asthma + Lung UK

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	to a product mentioned in the stakeholder list. This project was completed on 31/12/24. • GSK provided £55,000 in grant funding toward the Taskforce for Lung Health 2025. The Taskforce is a collaboration of over 40 key stakeholders looking to improve lung health in the UK. The Taskforce is funded by its Industries Forum. GSK's grant funding did not relate to a product mentioned in the stakeholder list. This funding is ongoing and is due to be completed on 31/12/25. • GSK provided a fee for service of £6480 + VAT to Asthma + Lung UK for their input into a survey around Oral Corticosteroids. GSK's funding did not relate to a product mentioned in the stakeholder list. This project is completed. • Asthma + Lung UK were the recipients of the GSK Impact Award in March 2024, and received an award of £1000. GSK's funding did not relate to a product mentioned in the stakeholder list. <u>Verona Pharma</u> • Verona Pharma provided £5,000 in grant funding toward the Taskforce for Lung Health 2024. The Taskforce is a collaboration of over 40 key stakeholders looking to improve lung health in the UK. The Taskforce is funded by its Industries Forum. Verona Pharma's grant funding did not relate to a product mentioned in the stakeholder list. This project was completed on 31/12/24. • Verona Pharma provided £5,000 in grant funding toward the Taskforce for Lung Health 2025. The Taskforce is a collaboration of over 40 key stakeholders looking to improve lung health in the UK. The Taskforce is funded by its Industries Forum. Verona Pharma's grant funding did not relate to a product mentioned in the stakeholder list. This project is ongoing and is due to be completed on 31/12/25 <u>Pfizer Limited</u> • Pfizer provided £30,000 in grant funding toward the Taskforce for Lung Health 2024. The Taskforce is a collaboration of over 40 key stakeholders looking to improve lung health in the UK. The Taskforce is funded by its Industries Forum. Pfizer's grant funding did not relate to a product mentioned in the stakeholder list. This project was completed on 31/12/24. • Pfizer provided £126,000 in grant funding toward Asthma + Lung UK's Winter Lung Health campaign. The campaign provided advice on how to stay safe and manage your respiratory condition effectively over the winter period. Pfizer's grant funding did not relate to a product mentioned in the stakeholder list. This project is now completed.

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We welcome the Committee's acknowledgement that Dupilumab will offer a new treatment for people with eosinophilic COPD. For many patients living with this lung condition, the current therapeutic approach does not meet all the needs of patients with COPD. There is a huge unmet need for many COPD patients, as too many on triple therapy still face significant lung function decline as the disease progresses. Many patients with eosinophilic COPD are trapped in a cycle of exacerbations. This has devastating consequences on their health and general well-being, with patients feeling hopeless, lonely, and scared. Every year, around 40,000 people die from COPD.[1] On average, one person dies from COPD in the UK every two minutes.[2] The UK has the worst death rate for COPD than anywhere else in Europe, apart from Turkey.[3] Last year, the European Medicines Agency approved Dupilumab for people with eosinophilic COPD.[4] We are concerned that if Dupilumab is not available to English COPD patients, this will mean that many patients' needs will continue not to be met, and the difference in COPD outcomes and mortality rates between the UK and the rest of Europe may be exacerbated. To reduce hospitalisations and mortality for this lung condition, patients with COPD desperately need new and effective treatments.

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2	We welcome the Committee's recognition that "moderate to severe COPD can substantially affect health-related quality of life." COPD and the resulting breathlessness have profound impacts on patients' lives. Many patients report that their breathlessness forces them to give up work. Every year, COPD causes reductions in productivity due to illness and premature death, totalling £1.7 billion annually in England.[5] 44% of COPD patients are below retirement age, and around one-quarter are not in work due to their COPD.[6] The Committee must consider the wider benefits that Dupilumab could bring for these patients and its potential to help many return to work.
3	We have heard from patients that they believe that this new treatment will give them hope for a better future. Many patients are not confident in the current treatments available, with one patient expressing that "the treatment that I'm on for my COPD doesn't feel to be particularly effective, and every day I struggle with breathlessness." Another patient who responded to our online survey said: "To be honest, I think my current meds are just like a plaster on a limp amputation." Dupilumab would be the first new treatment available to COPD patients in a decade. Patients living with COPD have told us that this new treatment gives them hope that they will have a "better life quality and will be able to manage this disease." Another patient told us they think this new treatment will "help reduce terrible breathlessness, making walking and doing everyday tasks easier." Research has shown that hope among COPD patients leads to improved treatment adherence, better condition management and reduced hospitalisations.[7]
4	We believe that the benefit of Dupilumab becoming available to patients in England has the potential to change how the system deals with people with COPD. Clinicians and patients have told us they hope that Dupilumab will bring attention to this respiratory condition, which does not receive adequate attention and prioritisation. People with COPD still struggle to access their essential basic care. A+LUK's 'Living with a Lung Condition' survey revealed that there is a huge unmet need for COPD patients and that only 10% of COPD patients in England reported receiving the 5 fundamentals of COPD care (smoking cessation, vaccination, pulmonary rehabilitation, personalised self-management plan, and optimising treatment for co-morbidities). [8] There have not been any new medicines for COPD in a decade. A new treatment, even though we expect only a small portion of COPD patients to be eligible, will hopefully drive local health systems to prioritise providing basic care for all COPD patients.
5	We believe that equality and deprivation considerations should be central to this technology appraisal. As mentioned above, too many COPD patients are not receiving their basic care, resulting in avoidable hospital admissions. Treating COPD costs the NHS £1.9 billion each year, with COPD being the second largest cause of hospital admissions and a significant driver of winter NHS pressures.[9] NHS performance is currently failing COPD patients. The poorest people with COPD have more exacerbations and are being left behind in terms of the care they are receiving. Those from the poorest 10% of households are 4.7 times more likely to die from COPD compared to the 10% most affluent households.[10] All COPD patients must receive good basic care to help them manage their condition effectively and reduce pressures on hospital emergency services. The Committee must consider how new medicines may improve the COPD care pathway and increase access to basic care for the COPD patients that need it most.

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NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 16th May 2025. Please submit via NICE Docs.

6	Dupilumab becoming available to COPD patients in England would reduce the burden from severe exacerbations on the NHS. COPD exacerbations account for one in eight UK hospital admissions.[11] There is a higher incidence of severe COPD exacerbations during the winter. COPD is estimated to account for 1.8 million annual hospital bed days in the UK, with 620,000 occurring during the winter period.[12] COPD prevalence is projected to rise by 40% by 2030, leading to rising NHS annual costs. The cost of COPD exacerbations is predicted to be £2.5 billion by 2030.[13] Reducing the number of severe COPD exacerbations will be vital to addressing the annual NHS winter crisis. For this to happen, patients must have access to their basic care alongside new treatments, such as Dupilumab.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterisks and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comment forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The

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comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

[1] International Respiratory Coalition, Chronic obstructive pulmonary disease, 2024. Accessed here.
[2] International Respiratory Coalition, Data from the UK by disease, 2024. Accessed here.
[3] Eurostat, Causes of death-standardised death rate by NUTS 2 region of residence, 2025. Accessed here.
[4] European Medicines Agency, Dupixent: Opinion on variation to marketing authorisation, 2024. Accessed here.
[5] Asthma + Lung UK and Taskforce for Lung Health, *Saving your Breath: Technical Report,* (2023) Accessed here.
[6] Adab P, Jordan RE, Fitzmaurice D, et al, Case-finding and improving patient outcomes for chronic obstructive pulmonary disease in primary care: the BLISS research programme including cluster RCT Southampton (UK), NIHR Journals Library (2021). Accessed here.
[7] Illness Perceptions, Cognitions, and Beliefs on COPD Patients' Adherence to Treatment: A systematic review, (17:3), Patient Preference and Adherence (2023). Accessed here.
[8] Asthma + Lung UK, *Life with a Lung Condition Survey* (2024). Data is available on request.
[9] Asthma + Lung UK and Taskforce for Lung Health, *Saving your Breath: Technical Report,* (2023) Accessed here.
[10] Asthma + Lung UK, COPD in the UK: Delayed diagnosis and unequal care, (2022) Accessed here.
[11] NHS England, Digital service to manage high-risk COPD patients, (2023) Accessed here.
[12] Asthma + Lung UK and Taskforce for Lung Health, *Saving your Breath: Technical Report,* (2023) Accessed here.
[13] NHS England, Digital service to manage high-risk COPD patients, (2023) Accessed here.

Single Technology Appraisal

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

Comments on the draft guidance received through the NICE website

Name	[redacted]
Comments on the DG: The NICE assessment concludes that dupilumab does not currently meet the cost-effectiveness threshold. However, this conclusion appears to rest on assumptions that underestimate the true mortality and disease burden in the target population. The mortality estimates used in the model are derived from the Whittaker study, which included a mixed, real-world COPD primary care cohort. That population was not selected based on inhaler therapy, blood eosinophil levels, exacerbation risk, or disease severity. In particular, the proportion of GOLD D patients—who are most likely to be eligible for dupilumab—was small. As a result, the model likely underestimates true mortality in the dupilumab-eligible population, which could artificially inflate the cost-effectiveness ratio. While NICE has called for more real-world data, such data already exists, including from the DECAF cohorts. These provide validated, event-based mortality estimates that are highly relevant to the frequent exacerbator subgroup targeted by dupilumab. Additionally, the model appears to assume that exacerbation rates remain constant over time, but this does not reflect clinical reality. There is strong evidence that exacerbations become more frequent and more severe over time, meaning the long-term benefit of dupilumab may be underestimated in the current model. Given these issues, the cost-effectiveness estimate for dupilumab is likely too high. With different—but still evidence-based and reasonable—assumptions, the intervention may well fall within the NICE cost-effectiveness threshold.	

Name	[redacted]
Comments on the DG:	
Association of Respiratory Nurses (ARNS)	

Has all of the relevant evidence been taken into account?
Unsure

Are the recommendations sound and a suitable basis for guidance to the NHS?
Yes

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
Not commented

Name	[redacted]
Comments on the DG:	

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The summary of the clinical effectiveness of Dupilumab appears to be a reasonable interpretation and importantly recognises the benefits in terms of exacerbation reduction, quality of life and lung function. While recognising the absence of a validated MCID for exacerbation reduction in COPD and that a 20% reduction is widely cited, much smaller reductions (4-11%) have also been cited as clinically meaningful in the literature. This reflects that a 20% reduction is a conservative value and that even lower magnitudes of reduction are considered by many to be clinically meaningful. Consequently, the magnitude of exacerbation reduction observed in both NOTUS and BOREUS in patients on otherwise maximal standard therapy are highly clinically meaningful.

With regard to the economic modelling, the challenge relates to the assumptions made and the apparent tendency of the EAG to underestimate the burden of COPD exacerbations and Dupilumab's potential impact.

It is critical to recognise the nature of COPD and the impact of exacerbations on subsequent disease course. It is well recognised that exacerbations are highly significant events for people with COPD. They not only dramatically impact individuals' lives, they contribute to driving disease progression through accelerated lung function decline, increasing risk of subsequent exacerbations (moderate and severe), increasing the risk of fatal and non-fatal cardiovascular events, and being associated with significant mortality risk. Even so-called mild exacerbations (i.e. those not resulting in treatment with steroids or antibiotics) can lead to lasting symptom burden with moderate and severe exacerbations having more significant impacts. While severe exacerbations are less frequent events, there frequency relates to that of moderate exacerbations and severe

exacerbations are typically observed less frequently in clinical trial cohorts than in the real-world. Additionally, the COVID pandemic led to around a 50% reduction in severe exacerbations during periods of enhanced public health protective measures (e.g. lockdowns), which will have impacted the ability to demonstrate differences in severe exacerbations in these trials. However, it stands to reason and makes clinical sense that the significant reduction in moderate exacerbations will translate into a reduction in severe exacerbations. Additionally, the marked mortality associated with exacerbations, particularly severe exacerbations, needs to be adequately considered within the eligible population. I agree with the clinical experts assertion that a median survival of ~13 years is entirely unrealistic within this population and that the model adopting SMR and the additional CFR is more aligned with expectations in practice.

Are the recommendations sound and a suitable basis for guidance to the NHS?

As a respiratory consultant, researcher, and clinical lead of a regional respiratory network, I do not feel that the current recommendation is sound and suitable guidance for the NHS.

COPD is the second commonest reason for emergency hospital admissions in the UK with hospitalisations highest during the winter months. These hospital admissions are a direct result of COPD exacerbations, and such events are therefore a major driver of healthcare resource utilisation and the pressure being experienced by acute NHS services. Additionally, COPD is significantly more prevalent among deprived communities with the impact of seasonal variation felt most acutely within this population. Consequently, recommending against the use of a drug that has been proven to be effective in reducing exacerbations, improving lung function and positively impacting quality of life appears entirely at odds with the needs of the health system and the drive to lessen inequities in health outcomes.

Dupilumab represents a well tolerated treatment for individuals with eosinophilic COPD who are otherwise on maximum available treatment and continue to exacerbate, providing a much needed therapeutic option. In addition to the clinical and health system benefits, exacerbation reduction has environmental co-benefits, with the majority of the environmental impact of COPD care being driven by exacerbation related healthcare resource utilisation. As such, the clinical benefits associated with Dupilumab are entirely aligned with NHS priorities and government policy.

Finally, Dupilumab is already available and NICE recommended for severe asthma and atopic dermatitis. While I recognise the EAG's need for clarification relating the health economic modelling, I find the arguments put forward troubling in relation to the apparent under recognition of the impact of exacerbations on disease progression and mortality. It is deeply concerning that these assumptions have the potential consequence of denying COPD patients, a cohort predominantly from deprived

communities, access to a treatment that has been shown to improve important, clinically meaningful outcomes.

Has all of the relevant evidence been taken into account?
There is a wealth of evidence available relating to the burden of exacerbations in COPD and their negative impact on patients' quality of life, their contribution to driving disease progression, the impact of blood eosinophils on risk, and their significant contribution to risk of important comorbidities (e.g. cardiovascular events) and mortality. Where there is absence of a specific study examining a specific question in the COPD sub-population of interest, it is necessary to draw on the breadth of related literature in order to make assumptions. This is what is being done for the health economic modelling and my feeling is that the wider literature is needed to sense check the assumptions being made. I agree with the clinical experts contributing to the consultation that a projected median survival of 13 years as proposed in the EAG base-case is entirely unrealistic within this COPD population and that the companies modelling achieves a more realistic estimate, and one that aligns more closely with the wider literature. I also feel that it is important to recognise that not all mortality relating to COPD exacerbation will be coded as such in observational data. For example, we know that there is a dramatically increased risk of cardiovascular events following COPD exacerbations (particularly severe exacerbations) and therefore CV deaths occurring in proximity to COPD exacerbations should also be considered potentially exacerbation related. Ultimately, these factors require consideration and it should be recognised that where data is lacking to enable direct quantification of these benefits within economic modelling, the lack of their inclusion within models is only likely to lead to underestimation of the benefits and therefore underestimation of the cost-effectiveness.

Name	[redacted]
Comments on the DG:	

Has all of the relevant evidence been taken into account?
No see below

Are the recommendations sound and a suitable basis for guidance to the NHS?

No, I do not believe so for reasons in the next answer

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No. I do not believe so. The sole use of the Whittaker data seems inappropriate here to use as the basis for the cost effectiveness. Whittaker its not a population that mirrors many that would potentially benefit from Dubilumab, such as those in the GOLD D group or patients with

eosinophilia/high feno being selected. You ask for more real world data- I would recommend looking at the DECAF score or PEARL score data, which is more relevant to a repeated exacerbator cohort. https://publications.ersnet.org/content/erjor/10/1/00838-2023.abstract. This metaanalysis also shows some data on UK inpatient mortality from Exacerbations of CPOD (6.9% - amongst the worst in the comparitor countries).

The whittaker paper itself, however, shows that 1/3 of all who died with COPD died within a month of an exacerbation - this is a horrifying stat and I can only presume has been overlooked by the committee when addressing the importance and benefits of reduction of exacerbations themselves, which Dupilumab can of course do.

Additionally, we know COPD exacerbations cluster and worsen over time as the disease progresses. Assumption that this will happen should be built into the model as the assumption exacerbation risk remains stable over disease progression is incorrect.

I therefore believe you have underestimated the effect Dupilumab could have, and that you have drawn incorrect conclusions about its cost effectiveness.

Are the recommendations sound and a suitable basis for guidance to the NHS?
Not currently

Has all of the relevant evidence been taken into account?
Re: Dubilumab, yes probably. But not re: selecting the right cost effectiveness cohort comparitor.

Name	[redacted]
Comments on the DG:	

Has all of the relevant evidence been taken into account?
Work has been undertaken to assess the financial and delivery impact of the introduction of these medicines for use in COPD and to generate insights and inform preparation at systema and Integrated Care Board (ICB) level to ensure appropriate access for eligible patients.

A key output of this work was to generate cost models for the different pathway scenarios to be able to compare the different requirements needed for the real-world1 scenarios compared to trial conditions. The model:

Determined the cost of the trial and two real-world pathways

Provided a breakdown of costs down by workforce, diagnostics and out-sourced services (e.g. homecare pharmacy administration costs)

Determined the cost implications of additional or higher cost clinical activities (such as delivering an appointment with a multi-disciplinary team (MDT) versus a single professional)

NHSE would like to share the outputs of this work for consideration by committee members.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No Response

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
yes it is reasonable.

NHSE would like committee members to consider the following findings.

Summary

Incremental per patient costs for the initiation & management of patients treated with dupilumab is between £1,198 (at the real world lower modelled scenario) and £2,937 (based on trial pathway conditions), excluding treatment costs for dupilumab.

Cost Modelling Approach

All pathways are based on dupilumab

Three scenarios are presented:

Trial Conditions

Real world upper

Real world lower

In terms of the preferred scenario in clinical practice, experts have advised it would be a blend of Real world (Upper) and (Lower) influenced by level of experience with asthma biologics.

The costing considers only the incremental / new costs occurring in the pathway to adopt Dupilumab.

The tables on the following pages have been calculated using the following assumptions:

Uptake Yr 1 = 8%, Yr 2 = 20%, Yr 3 = 30% (incremental, not cumulative)

Eligible population numbers based on NICE Budget Impact Assessment.

Table 1: Percentage population uptake per year Yearly Uptake

Eligible population

Percentage uptake

Numbers

Year 1

29,566

8%

2365

Year 2

29,862

20%

5972

Year 3

30,134

30%

9037

Totals

58%

17,374

Patient Level (In Year)

The table below outlines the simple per patient incremental costs associated for the three pathways (trial, real world (upper) and real world

(lower). Real world (upper) is defined as the highest potential costs associated with the real-world pathway and real world (lower) as the lower costed scenario (which includes more use of remote monitoring and nurse-led services).

In subsequent tables additional detail will be provided on the activity and cost volumes across years in line with Table 1

All cost assumptions are taken from NHS Cost Collection 2023/24 data unless otherwise stated. The homecare costs are associated with the administrative costs incurred by the trust; this cost was provided by Clinical pharmacists within the MVA team at NHSE.

Table 2: Per patient costings (In Year)

Picture 1, Picture

* Taken from figures cited in MVA Obesity Annex B calculations

~ Taken from NHSE estimation

Onward incremental cost assumptions – Year 2 & 3

Additional calculations were performed to consider the pathway costs for patients who remain on biologics beyond the first year on the treatment.

Pathway assumes: 1 annual face-to-face follow up with a nurse, one Full Blood Count (FBC) and homecare pharmacy administration costs (£809 per patient per year)

Cumulative costs

The calculations below assume the following:

100% of patients from Year 1 would continue into Year 2 (2365 patients)

100% of patients from Year 2 would continue into Year 3 (5972) plus the 2365 patients above = 8337 patients

The overall impact is an additional £8.7m costs across three years

These costs are integrated into each of the scenarios on the following pages.

Table 3: Cumulative costs

Picture 1, PicturePopulation level: Trial scenario

In this scenario the following assumptions are applied:

Year 1 Costs: £2,937 per patient + £809 recurring costs beyond year 1 for continuation

All patient contacts are face to face and Consultant led

There are nine reviews through the 52-week period (as per the trial pathway (letter M))

It is assumed a full blood count (FBC) is taken at each review (as there are nine listed in the Dupilumab trial protocol (BOREAS))

Chest x-ray/MRI is assumed to be used in all patients (100%)

Table 4: Population Level Clinical Activity Costs - Trial Scenario

Picture 2, PicturePopulation level: Real world scenario (Upper)

In this scenario the key assumptions are applied:

Year 1 Costs: £1,663 per patient + £809 recurring costs beyond year 1 for continuation

The assessment and decision to initiate Dupilumab will be taken by an MDT (consultant-led)

A nurse will administer the first two biologic dose in a clinic setting

The 6-month review will be by a consultant (remote)

The 12-month review will be performed by a consultant (F2F)

Table 5: Population level clinical activity & costs - Real World Scenario (Upper)

Picture 3, PicturePopulation level: Real world scenario (Lower)

In this scenario the key assumptions are applied:

Year 1 Costs: £1,198 per patient + £809 recurring costs beyond year 1 for continuation

The assessment and decision to initiate Dupilumab will be taken by a Respiratory Consultant (F2F)

A homecare nurse will administer the first two biologic doses in a home setting

The 6-month review will be Nurse-led (remote)

The 12-month review will be consultant-led (remote)

Table 6: Population level clinical activity & costs - Real World Scenario (Lower)

Picture 4, Picture

Capacity uplift from baseline

The current activity assumptions below have been taken from SUS data used within the National Cost Collection publication data 2023/24 for Summary Outpatient Appointments.

Total numbers based on the face-to-face activities for Consultant (including Consultant-led MDT) and Non-Consultant Care respectively for Department Description Service 340-Respiratory Medicine.

Activity baseline uplift calculations over three years (for trial, real world upper, real world, lower).

Table 7: Clinical activity uplift from baseline

Picture 5, PictureCOPD Biologics ICB Engagement Report

Summary of key findings

Funding: Significant concerns about the financial sustainability of introducing high-cost biologics, particularly given the increasing number of NICE Technology Appraisals and limited flexibility within ICB budgets.

Workforce: The majority view was that whilst the introduction of biologics in COPD would create additional capacity demands, it would not necessitate significant step change, new pathways could be delivered via creative care models utilising alternative roles that are not consultant led to realise the medicines' potential to reduce exacerbations and associated service demand. There was also an appetite to utilise the breadth of the multi-disciplinary clinical team such as nurses, pharmacists and GPs with extended roles.

Service Requirements: There was consensus that it was important to record and track prescribing of biologics. In particular, clinical outcomes should be

monitored to assess real-world benefits of biologics, though the process should remain light touch. Homecare is functioning well in most areas; however, concerns were raised about relying on it exclusively, due to issues with medication delivery and general instability of the market. Technology was mentioned as an enabler to streamline processes but also to provide additional clinical assurance.

Implementation: Implementation within 90 days of NICE appraisal was generally considered feasible, but national commissioning guidelines would be valuable to ensure a consistent and equitable rollout.

Name	[redacted]
Comments on the DG:	

Has all of the relevant evidence been taken into account?

Additional information should be considered:

1. Mortality modelling: The PEARL score was developed in 2,417 consecutive, unique patients with physician and spirometry confirmed COPD who survived an exacerbation requiring hospitalisation across six UK hospitals (patients with multiple admissions were only included once). Mortality was 9.7% (234) at 90 days (Ref: Thorax 2017;72:686-93 Supplement Table E3), and 23.2% (560) at one year (Ref: Thorax 2023;78:1090–1096).
2. Cardiovascular events, particularly myocardial infarction (MI), spike directly following exacerbations, rapidly falling afterwards. There is at least an 8-fold increase in MIs within 7 days of severe exacerbation (Ref: Rothnie. Ann ATS. 2018;15(8):935-956). In ETHOS, triple therapy reduced exacerbations and mortality, with the greatest reduction in both outcomes seen in patients with higher blood eosinophil counts. The mortality difference was largely due to fewer cardiovascular events. Exacerbations are associated with high oxidative stress and atherosclerotic plaques will be subject to increased shear forces, increasing the risk of plaque rupture (leading to MIs and strokes). Additional physiological processes during exacerbations are linked to major adverse cardiovascular events and death. Reducing exacerbations, particularly severe events, will also lead to a reduction in cardiovascular events and deaths.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I urge the committee to reconsider the recommendations. I have separately commented on the mortality model, providing high quality data on mortality, strongly challenging the EAG model. The strength of this cohort is substantially higher data quality, including certainty about diagnosis -

physician and spirometry confirmed COPD, and physician confirmed COPD exacerbation. I highlight the rationale for including major adverse cardiovascular events triggered by COPD exacerbation, and the higher admission rates post pandemic - a similar relative reduction in events will translate to a substantially higher absolute reduction in events and cost saving. It is not biologically plausible that moderate exacerbations are reduced but not severe events - the causes remain the same. Multi-morbidity, frailty and severity (inc due to delayed treatment) drive admission risk. Finally, this is a disadvantaged group. It is not NICE's job to correct deprivation, but it is within remit to ensure that this characteristic is not allowed to further increase health inequalities.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I have a few key concerns:
1. The EAG suggested median survival in the target population (13 yrs) is incompatible with the robust data in the large UK cohort of consecutive admissions with physician and spirometry confirmed COPD exacerbation highlighted above (one year mortality 23.2% - ref above). Allowing for a lower mortality in patients only experiencing moderate exacerbations, this strongly supports an expected median mortality between 4-7 years.
2. It is also reasonable to include a proportion of major adverse cardiovascular events as COPD exacerbation related events (note the large spike in the risk of such events immediately following moderate and particularly severe COPD exacerbations). Reducing COPD exacerbations will reduce cardiovascular events and deaths triggered by exacerbations.
3. The causes of moderate and severe exacerbation are the same; this is reflected in a similar proportional reduction in both. The lack of statistical significance is simply a matter of power.
4. Both RCTs were conducted during the pandemic when patients went to great lengths to avoid hospital admission. However, admissions for COPD exacerbation have since risen substantially.

As a consequence, the clinical and cost effectiveness of Dupilumab have been underestimated.

Has all of the relevant evidence been taken into account?

Both COPD and COPD exacerbations are strongly associated with deprivation (hospitalisation rates are 3-fold higher in the most deprived quintile compared to the least, and 6-fold higher in the most deprived decile compared to the least). This is a population already subject to health inequalities. Setting a higher ICER for interventions that reduce COPD exacerbations is justified; this will primarily benefit disadvantaged populations to address current inequalities. The wider societal impact of exacerbations, including productivity and carer burden are not captured but important to consider.

Name	[redacted]
Comments on the DG:	

Has all of the relevant evidence been taken into account?

No, the draft guidance does not fully account for all relevant evidence. While the BOREAS and NOTUS trials (NEJM, 2024; Sanofi, 2024) are highlighted, these studies represent a highly selected population with raised eosinophil counts (≥300 cells/μL). However, a systematic review (MDPI, 2024) and real-world data (Frontiers in Medicine, 2024) demonstrate that Dupilumab offers significant benefits across a broader range of patients, including those with lower eosinophil counts. Ignoring these data risks underestimating the therapy's full impact.

Are the recommendations sound and a suitable basis for guidance to the NHS?

The current recommendations are overly restrictive. This contradicts the growing body of evidence showing that Dupilumab provides clinically meaningful benefits across diverse COPD populations (MDPI, 2024; NEJM, 2024). The guidance fails to align with real-world patient needs and overlooks Dupilumab's potential to reduce exacerbations, improve lung function, and enhance quality of life.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No, the summaries of clinical and cost-effectiveness in the draft guidance are overly cautious. The reported improvements in exacerbation rates (31% reduction) and lung function (133 ml increase in FEV1) are clinically meaningful in the context of COPD, where even small reductions in exacerbations can prevent hospitalizations and reduce corticosteroid use (NEJM, 2024). The economic model also underestimates cost savings, as it does not fully capture the reduction in severe exacerbations and healthcare utilization demonstrated in real-world studies (Frontiers in Medicine, 2024).

Are the recommendations sound and a suitable basis for guidance to the NHS?

No, the recommendations are not sound as they are overly restrictive and fail to reflect the full range of evidence supporting Dupilumab's benefits. By limiting use to a narrow population defined by high eosinophil counts (≥300 cells/μL) and frequent exacerbations, the guidance overlooks the substantial benefits demonstrated in broader patient populations (MDPI, 2024; NEJM, 2024).

Has all of the relevant evidence been taken into account?

No, the draft guidance does not fully account for all relevant evidence. While the BOREAS and NOTUS trials (NEJM, 2024; Sanofi, 2024) are highlighted, these studies represent a highly selected population with raised eosinophil counts (≥300 cells/μL). However, a systematic review (MDPI, 2024) and real-world data (Frontiers in Medicine, 2024) demonstrate that Dupilumab offers significant benefits across a broader range of patients, including those with lower eosinophil counts. Ignoring these data risks underestimating the therapy's full impact.

Draft guidance consultation: Dupilumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease

Response from the COPD Consortium

The COPD Consortium is a multi-professional, multi-disciplinary group of clinicians who have a focus on COPD.

They consist of some of the world's leading COPD academics, clinicians as well as the leads of the National Respiratory Audit program and COPD workstream, NHSE respiratory leads and Chair of the BTS. They represent a wide geographic coverage right across England.
The names of the members are at the end of this response.

The consortium was pleased to be asked to respond to the NICE TA for Dupilumab in COPD both as a group and as individuals. Please find some detailed comments on the draft guidance and the process undertaken thus far.

General Comments:

Overall, the guidance is welcome, but we have concerns about several aspects of the methodology utilized and thus the conclusion reached, especially with the focus on mortality which was not a measured endpoint in the pivotal studies and thus is open to a wide range of interpretation.

Making the assumption that exacerbations do not have an incremental effect of mortality risk is wrong as has been shown in seminal studies by Suissa et al (Suissa 2012) and more recent work such as the Pearl study and the work by Rothnie et al.

We are also concerned that in comparison to the use of Dupilumab in TA751 for severe asthma, as a third line therapy, the ICER was set at a very different level to that of Dupilumab in COPD. This seems on the face of it as if the NICE TA is placing different values on treating patients with different diagnoses.

The third significant focus of our comments are that the TA committee have not considered health inequalities as a significant issue for people living with COPD, nor that this may be helped by the provision of Dupilumab. Inequality in COPD is not just about protected characteristics but is much more about

deprivation and ability to access and utlise healthcare. Race and culture do play a part and need to be considered, but COPD prevalence, morbidity and mortality is tightly associated with deprivation in England. The provision of Dupilumab will enable a new approach to COPD to be taken by healthcare providers and by democratizing delivery (as proposed by the NHSE, Medicines Innovation, Innovation, Research and Life Sciences Strategy.

A treatment that reduces exacerbations and especially reduces hospitalisations will have significant effects on beds (especially during the Winter) and thus potentially unblock hospitals during critical times. It is hard to estimate the size of this effect as it will depend on the roll out of dupilumab but would be of the order 5000 bed days per 1000 patients treated. This consideration for the whole impact of improving the outcomes in COPD is both relevant and critical.

Detailed comments.

Page 4. Section 1.2
Uncertainties around mortality data

We do understand why mortality is a key outcome when looking at the modelling for the ICER and the use of Dupilumab however there are concerns that in choosing this for COPD and not part of the consideration of for other appraisals. We believe that in this NICE are disadvantaging protected groups. By looking at the impact of a metric that was not the primary outcome of the trials, then, the committee are disadvantaging those who are disabled with COPD.

1. By prioritising mortality as a primary issue it seems that the committee is taking a very different approach to that taken in other airway diseases (e.g. TA751 for severe asthma). Here the primary outcome was the one for which impact was funded (i.e. reducing exacerbations). Moreover, it seems that there is a different ICER being utilised between asthma and COPD (20k vs 28k). COPD patients are greatly disabled, and mo If severe exacerbations and mortality are the outcomes for which the committee will entertain impact/cost-effectiveness, re so than asthma patients. So, here the committee are disadvantaging people with a disability and actively making the threshold harder to attain.

2. If severe exacerbations and mortality is the outcome, for which the committee are using to calculate impact/cost-effectiveness, then assumptions based on the best available evidence needs to be considered and added into the model. One person dies with COPD every 20 mins (Asthma and Lung UK data). One person is admitted with COPD exacerbation every three minutes (NICE data) and one person has an exacerbation every 20 seconds (Primary Care Respiratory Society). By reducing exacerbations (the PCRS data), you will impact the NICE data and then impact the ALUK data. This is logical.

3. Each exacerbation (moderate) leads to risk of severe exacerbation and death (Donaldson Chest 2010; Soler-Cataluña 2005; NRAP 2024. These are cumulative and increase over time in impact and frequent (Suissa 2012).

4. The PEARL score was developed in 2,417 consecutive, unique patients with physician and spirometry confirmed COPD who survived an exacerbation requiring hospitalisation across six UK hospitals. Mortality was 234 (9.7% at 90 days (Echevaria, Thorax 2016;72:686-93 Supplement Table E3), and 560 (23.2%) at one year (Echevaria Thorax 2023;78:1090–1096). This data is new and UK data that can inform a review of the real post-covid median survival data.

5. Cardiovascular events, particularly myocardial infarction (MI), spike directly following exacerbations, rapidly falling afterwards. There is an 8-fold increase in MIs within 7 days of severe exacerbation (Rothnie. Ann ATS. 2018;15(8):935-956). In ETHOS, triple therapy reduced exacerbations and mortality, with the greatest reduction in both outcomes seen in patients with higher blood eosinophil counts. The mortality difference was largely due to fewer cardiovascular events. Exacerbations are associated with high oxidative stress and atherosclerotic plaques will be subject to increased shear forces, increasing the risk of plaque rupture (MI). Additional physiological processes during exacerbations are linked to major adverse cardiovascular events and death. Reducing exacerbations, particularly severe events, should also lead to a reduction in cardiovascular events and deaths.

6. The EAG suggested median survival in the target population (13 yrs) is incompatible with the robust data in a large UK cohort of consecutive admissions with physician and spirometry confirmed COPD exacerbation (one year mortality 23.2% - ref above). Allowing for a lower mortality in patients only experiencing moderate exacerbations, this strongly supports an expected median mortality between 4-7 years. As highlighted, it is also reasonable to include a proportion of cardiovascular deaths as COPD exacerbation related events; reducing exacerbations will reduce cardiovascular events.
This is more in line with other data including the HES data on COPD that was collected pre-covid as well as the data from Rothnie et al (2018).

All of this is strong evidence that supports a significantly increased level of mortality in the high-risk patients with COPD who are experiencing exacerbations. Each exacerbation has a consequence which increases both direct mortality but subsequent indirect mortality due to cardiac disease.

Duration of Benefits of Dupilumab

The Boreas and Notus studies demonstrated significant clinical benetifs which started as soon as the drug was administered. There was no sign of drop off of effect and the effect continued as long as the drug was administered. There is no reason to assume that this would not continue, the underlying biology has not been altered and neither had the pathological changes in spite of improvements in lung function. There is clear evidence that supports long term impact on lung function decline. Type-2 inflammation is associated with

accelerated FEV_1 decline in individuals with chronic airway disease and is improved by targeted intervention such as Dupliumab. (Çolak Y, 2024),

Evidence to support long term impact on lung function decline. Type-2 inflammation is associated with accelerated FEV_1 decline in individuals with chronic airway disease
Type-2 inflammation and lung function decline in chronic airway disease in the general population | Thorax

P5. 2.5
Carbon impact

Poor disease control is bad for the environment and a hospital admission very much worse. Good control of chronic disease leads to lower carbon footprints for healthcare and as such Dupilumab will reduce carbon impact. Moreover, as this drug can also be self-administered in the patient's home (Bell 2021).

Generally, there is an estimated carbon footprint of 125 kg CO2e per hospital bed-day and 76 kg CO2e per outpatient appointment for acute care, 66 kg CO2e per general practice visit, and 75 kg CO2e per ambulance emergency response, among others (Wilkinson 2020)

Hence, keeping patients healthy and their lung disease well controlled is important to minimise preventable worsening and health resource utilisation; this is beneficial for both patient and planetary health

P5 3.1
COPD exacerbations are central to the disease as a characteristic of the disease and are not a symptom of the disease as described here.

We do not grade COPD by numbers but mild, moderate, severe and very severe. Each carries an increased risk of exacerbation and death.

P6 3.2
Azithromycin use has dramtically increased ove the last 10 years and carries with it significant risks of harm as well as an increased level of resistance. This is of great concern to the medical microbiological community (Lu 2022).

P10 3.5
Impact of Covid
It is likely that as covid had a marked effect on exacerbations and especially on admissions to hospital then the effect of Dupilumab may have been underestimated in the pivotal studies (Lam 2024)

P12 3.6
Effect on FEV1.
Any improvement in lung function will result in a clinically meaningful change, especially as COPD is a disease which by definition is irreversible. The MCID for FEV1 for inhaled therapies is 100ml, Dupilumab demonstrated greater improvements than this on top of optimal inhaled therapies.

P12 3.6
Effect on exacerbations.
It is widely acknowledged, and a consensus has been reached that a 20% reduction in exacerbation rate is meaningful (Chapman 2013). Indeed, many believe that 11% is reasonable. The TA draft is in error on this point.

P15 3.9
Exacerbations
The fact that the majority of exacerbations were moderate is due to the effect of covid and the marked change in illness behaviour and hospitalisation seen during this period.

P21 3.11
Mortality and value
There is certainly a link between exacerbations and all-cause mortality in COPD however we believe that the cost effectiveness should be more weighted towards the exacerbation (moderate and severe) reduction rather than the subsequent modelling for mortality benefit which relies on assumptions. That said – the CFR added to the SMR does seem to more accurately reflect real world mortality data in COPD – we know that mortality 4 years after first hospitalisation with an exacerbation of COPD is 50% and in patients having Non-invasive ventilation during their exacerbation admission, the 1-year survival is 50%.

P23 3.15
ICER
The acceptable ICER of £20 000 for Dupilumab in COPD agreed by the committee is markedly different to the ICER chosen by NICE for the use of Dupilumab in severe asthma (£28 929), NICE TA 751, section 3.21 and also noting for atopic dermatitis TA534 (ICER of £27-28k) too. There should be parity for the same drug used across different indications. Additionally, as mentioned in the NICE manual, an ICER falling between (and not exceeding) the threshold of £20-30k is usually deemed as cost effective by NICE, hence the approach taken for the decision is inconsistent

It is important to note that the committee has not considered in the economic model the costs of current treatment of exacerbations. The use of oral corticosteroids is associated with significant harm and healthcare cost. The use of Dupilumab will reduce this used and reduce cost as well as leading to the avoidance of the long-term harm of oral cortico-steroids. Potentially underestimating the benefit of this new therapy.

P25 3.18
Equality
Whilst the group does not disagree with the legal responsibilities that NICE has with regards to Equality it seems that this TA is missing an opportunity to reduce inequalities and provide a treatment that will effect a generational change in the overall management of COPD. Reversing the huge nihilism that exists around this disease that leads to patients feeling helpless and alone

and doctors feeling that there is nothing they can do for patients will be a huge step forward in reducing inequality of the provision of care.

Overall, we worry that the outcome of this TA may widen inequalities outside of protected characteristics, which aren't being considered as part of equalities impact assessment here and also not in line with what is published on NICE development process:

When forming its recommendations to NICE, the committee considers those factors it believes are most appropriate for each evaluation. In doing so, the committee takes into account the provisions and regulations of the Health and Social Care Act 2012 relating to NICE, and NICE's legal obligations on equality and human rights. The Act expects NICE, when doing its general duties, to be aware of: the broad balance between the benefits and costs of providing health services or social care in England, the degree of need of people in England for health services or social care, the desirability of promoting innovation when providing health services or social care in England.'

The consortium believe that if approved by NICE that it would be important to recommend that a COPD biologics registry is established as a requirement.

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Members of the COPD Consortium are:

[redacted]

[redacted]

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

EAG response to stakeholder engagement

June 2025

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1 Introduction

Following the first appraisal committee meeting (ACM1) for dupilumab, the committee highlighted key areas of uncertainty relating to the magnitude of the reduction in severe exacerbations, long-term treatment effect and the modelling of mortality. In order to determine the most plausible ICER, the committee requested further evidence on the following:

1. Whether the magnitude of reduction in severe exacerbations in BOREAS and NOTUS was applicable to clinical practice.
2. Support of a maintained treatment benefit for dupilumab compared to background therapy for the lifetime of the model.
3. Data on real-world survival for the population covered by the evaluation to inform the model and validate survival outputs from the model.
4. Data estimating how much of the mortality in the population covered by the evaluation is due to exacerbations.
5. Support for applying a case fatality rate (CFR) to account for the increased risk of mortality from exacerbations in addition to the standardised mortality ratio (SMR) to estimate mortality associated with COPD severity.
6. Alternative sources of evidence for the CFR.
7. A scenario analysis applying a CFR due to exacerbations without the application of SMRs, or any other adjustment for mortality.

The committee also noted their preferred assumptions for two model inputs:

- Transition probability between COPD severity health states informed by Fenwick *et al*. with an additional adjustment using a multiplier for EOS≥300, as per the company base case.
- Non-treatment specific utility values, informed by trial data of mapped SGRQ to EQ-5D-3L (cross-walked) using statistically significant covariates only, as per EAG base case.

Section 2 of this report provides the Evidence Assessment Group's (EAG's) response to the evidence supplied by the company in response to each of the committee's requests highlighted in the draft guidance. In addition, the EAG provides cost-effectiveness results of additional scenario analysis conducted by the EAG in Section 3.

2 EAG response

2.1 Magnitude of reduction in severe exacerbations

The committee considered that dupilumab was likely to result in a reduction in severe exacerbations compared to standard of care (SoC) but highlighted how the magnitude of this reduction is uncertain due to the low number of severe exacerbations in the BOREAS and NOTUS trials. They also requested further evidence to demonstrate that the magnitude of these reductions were applicable to clinical practice.

In their response (Section 1.1), the company highlighted how there are fewer severe exacerbations with dupilumab than standard of care (SoC) in the trials, and that the difference between trial arms is close to the threshold for statistical significance (p=0.0725). The EAG agrees with these conclusions but does not believe this addresses the uncertainties about the magnitude of the reduction in severe exacerbations with dupilumab.

The company reported that the effect estimate for the annualised rate of severe exacerbations favours dupilumab over SoC (RR 0.674; 95% CI: 0.438 to 1.037) and suggested that the 95% CIs indicate a strong trend in the reduction of severe exacerbations with dupilumab. However, the EAG considers that these wide 95% CIs instead reflect considerable uncertainty when interpreting the extent to which severe exacerbations are reduced with dupilumab. Based on the effect estimate, the company reported that dupilumab results in a 32.6% reduction in severe exacerbations compared to SoC, but the EAG notes that the 95% CIs indicate that the difference between trial arms could plausibly range from a 56.2% reduction to an increase of 3.7% with dupilumab. As such, the precise magnitude of the reduction in severe exacerbations with dupilumab remains uncertain.

One of the factors leading to uncertainty in the results is the small number of severe exacerbations experienced in the BOREAS and NOTUS trials. This may have been impacted by the timing of the trials, which took place during the COVID-19 pandemic, when many people with COPD experienced fewer exacerbations.[1] The company noted that clinical experts also reported that many severe exacerbations may have been inappropriately recorded as moderate events during the pandemic due to patients' concerns about attending hospitals during this period. To address the low numbers of severe exacerbations, and concerns about the misrecording of exacerbation severity, the company presented a tipping-point analysis to estimate how many moderate exacerbations in the SoC arm would need to be reclassified as severe to result in a significant difference between

dupilumab and SOC. When six of the 698 moderate exacerbations in the SoC arm were reclassified as severe, a statistically significant difference (p=0.045) was seen between trial arms. However, it is unclear why this analysis only considered reclassification of exacerbations in the SoC arm, and the EAG is unaware of any reason why exacerbations would be less likely to be misclassified in the dupilumab arm. In addition, while the tipping point analysis demonstrates that the results may be sensitive to the wrong classification of exacerbations, it does not address the uncertainty reflected in the wide 95% CIs nor does it help inform the precise estimate that should be used to reflect the reduction in severe exacerbations with dupilumab compared to SoC.

Other analyses were reported by the company, including severe exacerbations and time to first severe exacerbation for patients who had the opportunity to reach 52 weeks of treatment and were still on initial treatment. However, the EAG notes that these are *post-hoc* analyses which break randomisation and no longer reflect the full ITT population. Instead, they more closely represent a per-protocol analysis, which can overestimate the treatment effect, and does not appear to address the uncertainties highlighted by the committee.

The company stated that the 32.6% reduction in severe exacerbations observed in the BOREAS and NOTUS trials was directly applicable to UK clinical practice as the benefit was observed in the population of interest. While the EAG agrees about the relevance of the population, it notes that other factors led to the committee's concerns about the applicability of the results. As outlined above, the COVID-19 pandemic means that it was likely there were fewer exacerbations during the trials than would usually be expected in clinical practice. In addition, the small number of severe exacerbations contributed to uncertainties about the magnitude of the reduction in severe exacerbations with dupilumab. Without further evidence, the EAG considers that uncertainties remain about how closely the reductions in severe exacerbations that were observed in the trials reflect what would be seen in clinical practice.

In the economic model, as exacerbations are split between COPD severity stage, the company did not apply a single rate ratio (RR) from the primary trial outcome to estimate the rate of exacerbations in the dupilumab arm. Instead, individual RRs based on the annual rate of moderate or severe exacerbations observed in the pooled trials in each COPD severity group were calculated, as shown below in Table 1 and previously presented at the first committee meeting.

Table 1. Calculated rate ratios for all dupilumab patients and dupilumab responders only, used to represent treatment effect

COPD severity	Dupilumab + background therapy (all patients)		Dupilumab + background therapy (responders only)	
	Moderate exacerbation	Severe exacerbation	Moderate exacerbation	Severe exacerbation
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]
Very severe	[redacted]	[redacted]	[redacted]	[redacted]

*Assumed to be the same as severe due to no exacerbations for very severe patients observed in the dupilumab arm
Abbreviations: COPD, chronic obstructive pulmonary disease.

The rates for dupilumab responders are used to inform the annual exacerbation rates for dupilumab in the long-term Markov model. As can be seen in the table, the calculated RR shows the strongest effect of dupilumab in the moderate to severe COPD groups for severe exacerbations and this is much larger than the reported reduction in all severe exacerbations noted by the company of 0.674. Splitting the patients based on COPD severity will have reduced the small numbers in each group with a severe exacerbation even further, increasing the uncertainty.

Overall, the EAG agrees with the statements of the company that a reduction in the number of severe exacerbations will have benefits for resource use in the NHS. However, while the analyses presented by the company indicate that dupilumab is likely to result in fewer severe exacerbations than SoC, the analyses do not address the uncertainties relating to the magnitude of these reductions. As such, the EAG considers that the true effect of dupilumab for reducing severe exacerbations in comparison to SoC remains uncertain. Other concerns, such as the impact of COVID-19 on exacerbation rates during the trials, mean it also remains unclear how relevant the results for severe exacerbations are to NHS clinical practice.

As stated in the draft guidance, experts consulted by the company and supported by clinical experts at the committee meeting, the mechanism for moderate and severe exacerbations is broadly similar and the rate reduction would be expected to be similar. The EAG notes that the magnitude of the reduction in the economic model for severe exacerbations is much larger than that applied for moderate exacerbations, as shown in Table 1. To reduce the impact of the uncertainty surrounding the magnitude of the reduction in severe exacerbations, the EAG consider it more appropriate to

apply the rate ratios derived from moderate exacerbations for each COPD severity, shown in Table 1, to severe exacerbations in the updated base case (see Section 3). The EAG notes that this is still considered optimistic based on the previous points noted regarding the uncertainty. The EAG notes that its preference would have been to apply RRs for each COPD severity based on the combined moderate and severe exacerbations, split between all dupilumab patients and responders only. However, the EAG did not have access to these data.

2.2 Maintained treatment benefit for dupilumab compared to background therapy

In the absence of long-term data for the effects of dupilumab for people with COPD, data from the TRAVERSE study for people with moderate or severe asthma was used as a proxy in the model. The committee considered this to be a reasonable assumption but were concerned that the company had not provided evidence to support the treatment effect being maintained for the duration of dupilumab treatment. More evidence was therefore requested from the company to support this assumption.

The company performed additional analyses to support the applicability of the asthma population, and the assumptions made about long-term benefits while on treatment. The company response includes an exploratory matching exercise, which appears to be based on applying propensity score weights, to demonstrate the long-term benefits of dupilumab when the TRAVERSE population were adjusted to match those from BOREAS and NOTUS. The results of four analyses were provided, which adjusted for the following factors:

1. Age, pre-BD FEV_1;
2. Age, pre-BD FEV_1, cardiac disorders;
3. Age, pre-BD FEV_1, vascular disorders;
4. Age, pre-BD FEV_1, respiratory disorders.

The company reported that the analyses were based on matched adjusted indirect comparison methodology, a key assumption of which is the adjustment of all prognostic factors and treatment effect modifiers.[2] However, with the separation of the three comorbidities into different analyses, this assumption is unlikely to have been met. It is also unclear to the EAG why age, pre-bronchodilator FEV_1 and the selected comorbidities were the only factors chosen for matching, and whether others were also considered. Without this information, uncertainties remain about

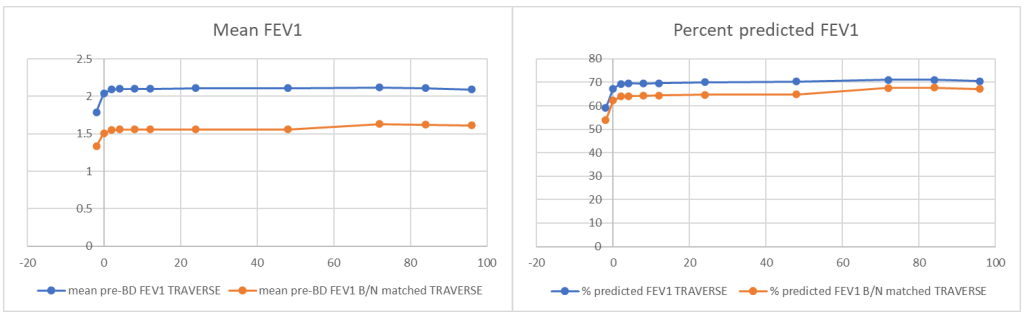
underlying differences that may exist between the two populations, despite the adjustments performed by the company.

Following adjustment of the TRAVERSE population, most of the baseline characteristics reported in the company's response were similar to those of BOREAS and NOTUS. However, there was a clear discrepancy in sex, where 66.8% of patients in BOREAS and NOTUS were male compared to between 32.2% and 34.5% for TRAVERSE. Any interpretation of these results should therefore consider whether sex is likely to have had an impact on response to treatment. In addition, the EAG notes that no baseline characteristics were provided for the comorbidities that were adjusted for in the analyses, leaving uncertainties about how effective the adjustments were for each of these factors.

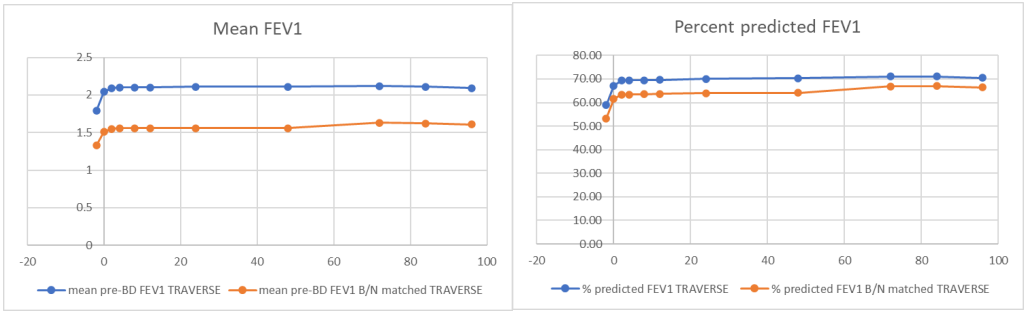
Each of the four adjusted data sets resulted in a lower mean pre-bronchodilator FEV_1 and lower percent predicted pre-bronchodilator FEV_1 than the unadjusted TRAVERSE population (Figure 1). Both outcomes followed a similar trend to the unadjusted population, remaining relatively stable across 96 weeks of treatment. While it is reassuring that the adjusted data sets indicate a sustained benefit of dupilumab, limitations of the analysis outlined above mean it is difficult to draw strong conclusions on how well this reflects the long-term benefits expected for patients with COPD. The EAG considers that confidence in the applicability of the TRAVERSE population could be increased with the provision of further information, including an analysis which adjusts for multiple comorbidities, further information about the choice of patient characteristics selected for matching, and additional baseline characteristics to assess the effectiveness of the matching.

Figure 1. Comparisons between the unadjusted TRAVERSE population and the adjusted populations matched on (A) age and pre-BD FEV_1, (B) age, pre-BD FEV_1 and cardiac disorder, (C) age, pre-BD FEV_1 and vascular disorder, (D) age, pre-BD FEV_1 and respiratory disorder. Reproduced from Figure 1 of the company's response.

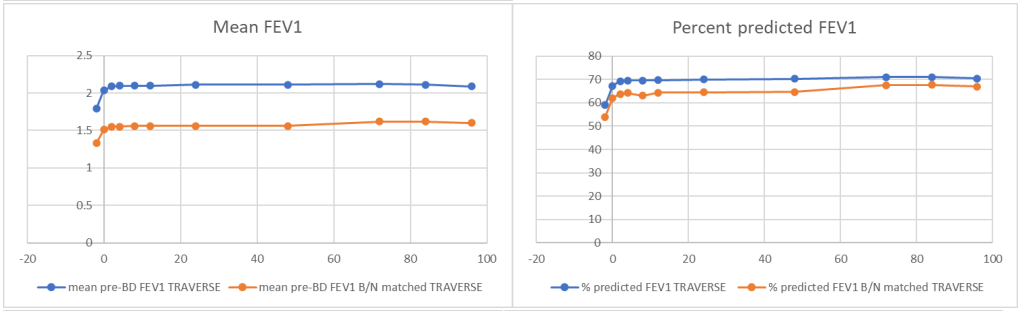
A.



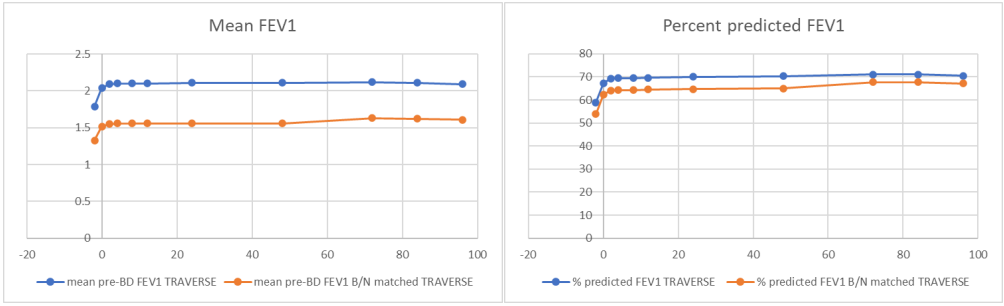
B.



C.



D.



The economic model applies a treatment effect of dupilumab both through COPD severity and exacerbations. While the company assumes the same transitions between COPD severity states as background therapy only after three years, the difference in treatment effect remains as patients in the dupilumab arm are distributed across less severe health states than patients in the standard of care arm. In addition, the EAG also notes that in the economic model, the treatment effect on the annual rate of exacerbations remains for the lifetime of the model while patients remain on dupilumab.

2.3 Real-world survival for the population covered by the evaluation

The company provided a range of analyses to support the survival estimates predicted by the economic model compared to median survival estimates from real-world data (RWD). Due to a lack of published real-world survival estimates for the specific population of interest (patients with uncontrolled COPD with Type 2 inflammation receiving triple therapy), the company aimed to match

the population from the RWD sources to the population of interest as closely as possible. The three key RWD sources used by the company were analyses of English Hospital Episode Statistics (HES) from 2010—2019, five year mortality data from the French BREATH study from 2015, and mortality data from the USA MarketScan database between 2018—2022. The EAG has reproduced a table provided by the company below showing a comparison of key characteristics of the three main analyses alongside the BOREAS/NOTUS pooled trial data. The EAG has also added the predicted median survival for patients on current standard care from each of the company's analyses.

Table 2. Key characteristics and median survival ok key real-word data analyses performed by the company

Characteristic	Study			
	BOREAS/NOTUS pooled	England – HES database analysis	France – BREATH study	USA – MarketScan database
Age, years	65.1	69.97	68.88	Age range used for the analysis is 65-74
Sex (male), %	66.8	56.02	60.76	45.08
Current smoker, %	29.8	50.39	N/A	N/A
Estimated median survival, years	8.3*	6.9	8.7	8.5

* Median survival from company's updated economic model which is based on the BOREAS/NOTUS pooled trial data

Abbreviations: HES, hospital episode statistics; USA, United States of America; N/A, not available

As detailed by the company in their response, there are a number of limitations and issues with the generalisability of each estimate of median survival due to the available data. The most applicable analysis to the current appraisal is the HES dataset which included a cohort of 3,747 patients in England closely matched to the inclusion criteria of the BOREAS/NOTUS trial population (COPD patients in England who had raised EOS ≥300 cells/µL, on triple therapy and had ≥2 moderate or ≥1 severe exacerbation in the previous year). However, no time-dependent mortality data were available and therefore the company calculated the median survival by assuming an exponential decline to give an estimate of median survival of 6.9 years. The EAG notes that for a progressive disease such as COPD, an exponential model is unlikely to be fully representative of mortality over time, with an increasing hazard considered more plausible, as suggested by the company in the analysis of the French BREATH study. Without time-dependent mortality data in the HES dataset

available, it is unclear to what extent alternative assumptions regarding the long-term hazard would impact the median survival estimates.

The EAG notes that comparisons of the median survival from the conducted analyses to the model-based outputs using the pooled BOREAS/NOTUS trials are uncertain due to differences in key characteristics between the populations. As seen in Table 2, the average age of patients in the pooled BOREAS/NOTUS trials, and therefore informing the model, was 65.1 years. The average age of patients in the HES and BREATH study datasets is 69.97 and 68.88, respectively. Based on this, the company used the dataset for patients aged 65 to 74 to predict the median survival for the USA MarketScan analyses. These differences are likely to influence the median survival estimates, as are differences in the proportion of patients who were current smokers, with 20% less being a current smoker in the trial/model population than the HES analysis. In addition, there are noticeable differences in the proportion of male patients between the different populations. In the UK general population, male mortality rates are typically higher than female. There appears to be mixed evidence on sex differences in mortality in the COPD population. However, a recently published study (Whittaker *et al.* 2025)[3] examining sex differences in asthma and COPD hospital care, readmissions and mortality using data from the National Asthma and COPD Audit Programme (NACAP) in England and Wales found females had lower odds of 90-day mortality that males.

The EAG acknowledges the limitations in the literature and RWD available on survival in the specific population of interest and considers that the additional analyses undertaken by the company do not invalidate the company's model estimates. However, there are a number of limitations with all analyses conducted, and therefore comparisons should be considered with caution.

2.4 Mortality due to exacerbations

In order to help validate the model outcomes when using the company's approach to modelling mortality, i.e. SMRs and separate CFR for severe exacerbations, the committee requested data estimating how much of the mortality in the population covered by the evaluation is attributable to exacerbations.

Based on the population identified from the HES dataset analysis previously discussed in Section 2.3, which was closely matched to the trial population, the company estimated the proportion of deaths attributable to exacerbations. Based on 1,522 deaths in the population during follow-up, 601 were related to exacerbation (39.5%). The company noted that this aligned with the updated base-case

model in which 41% of mortality was related to exacerbations and 53% due to COPD severity stage. It is noted that this this does not add to 100% as it is based on deaths occurring in the Markov section of the model only (i.e. excluding the one-year decision tree) as it is not possible to attribute the source of deaths in this section. The EAG notes therefore, that, of the 94% of deaths in the Markov model, 43.6% were due to severe exacerbations, while the remaining 56.4% were due to COPD severity.

The EAG considers it reassuring that the proportion of deaths from exacerbations in the model is largely in line with the HES dataset. However, it is noted that the same caution may need to be applied when comparing model outputs to the RWD analysis, as discussed in Section 2.3.

2.5 Support for applying a case fatality rate (CFR) in addition to standardised mortality ratio (SMR)

In response to the request for further evidence to support applying a CFR in addition to SMRs related to COPD mortality, the company provided a range of data (Section 5 of the company response). The company provided references to four recently published cost-effectiveness analyses for COPD in which both an SMR related to COPD severity and a separate CFR for exacerbations are applied. On consideration of these studies and the impact of severe exacerbations on mortality, as discussed from other stakeholders during consultation and during the committee meeting, the EAG considers the approach used by the company to be justified. The EAG notes, however, that the main issue is the potential for double-counting the impact of exacerbations on mortality in the economic model with the sources used by the company to inform the SMRs and CFR.

In response to the potential of double-counting the impact of severe exacerbations using Whittaker *et al.* 2024[4] to inform the SMRs based on COPD severity and a separate CFR, the company provided further details regarding the number of severe exacerbations in the Whittaker study population. This showed that, of the patients included, only 4.3% had one or more severe exacerbations in the year prior to baseline (14,603 patients with ≥1 severe exacerbation ÷ 339,647 total patients with COPD). The EAG also recognises that the COPD population in the Whittaker study is less severe than the population under consideration in this appraisal and therefore applying only these SMRs, with no separate consideration of exacerbations, may overestimate survival. While the EAG considers that

population in Whittaker *et al.* may not be fully representative of that in the economic model, it is considered the most appropriate of those available.

The EAG is reassured that the proportion of severe exacerbations in the Whittaker population was very minimal. Based on the small proportion of patients who had severe exacerbations, the EAG acknowledge that the proportion of patients who would die as a result of this is also likely to be even smaller. Therefore, while still possible, the EAG consider that the risk of double-counting the impact of mortality through a separate CFR for severe exacerbations should be very small.

2.6 Alternative sources of evidence for the CFR

Regarding the economic modelling of mortality, the committee also requested alternative sources of evidence for the choice of CFR applied, if a separate CFR was supported by the evidence. The company maintained that the CFR sourced from Hoogendoom *et al.* 2011[5] was the most appropriate to use in the economic model; this is a CFR of 15.6%. The company also discussed a range of alternative options for the CFR and why these were not appropriate.

The company state that 15.6% is appropriate as it avoids the use of any arbitrary time cutoffs, such as that used by NACAP 30/90-day rates, and only captures the excess risk of mortality due to severe exacerbations and excludes any background mortality due to other causes. The company states that using 90 survival data from the NACAP data, specific to the UK and Wales, is not appropriate as published evidence supports that the mortality impact of a severe exacerbation can be much longer than 90 days and therefore the true CFR would be expected to be higher than 11.9% NACAP estimate.[6] The company references Wildman *et al.* 2009 in support of this, which gives 180-day mortality of 37%.[7] This study was based on patients admitted with an exacerbation to an intensive care unit (ICU) or a respiratory high dependency unit. Therefore, this population is not reflective of all severe exacerbations and is likely to reflect the most severe patients who would be expected to have a higher mortality rate.

In response to the EAG's concerns regarding the applicability of the studies included in the Hoogendorn meta-analysis, the company stated that the acute treatment of severe exacerbations has not changed considerably in the past 20 years and so the impact on mortality should be minimal, which is shown through no change in the NACAP 90-day mortality rates from 2014 and 2023. The company also notes that mortality figures in England are considerably worse that almost all other European countries and therefore the estimate may be an underestimation of the risk of UK

exacerbation mortality. The EAG remains concerned with the applicability of the studies as the best estimate for a UK population, as it is noted that 2005 was the most recent data used in the included studies, while all others are based on data from 1999 and prior. While the EAG acknowledges the higher rates of mortality in the UK compared to other European countries, this is not the case for Turkey, and Denmark also has a similar rate to the UK.[8] Turkey and Denmark were included in the six studies informing the meta-analysis. Two of the six studies were based in the USA. The EAG acknowledges that UK clinical practice may not have substantially changed and that the UK has high mortality rates; however, the EAG does not consider it appropriate to state that the CFR in Hoogendorn may be an underestimate.

The company also presented results from using the incidence rate ratios (IRRs) related to both moderate and severe exacerbations from Whittaker *et al.* 2022.[9] The company notes that these are not appropriate to measure the excess mortality related to exacerbations as they are applied to the Whittaker *et al.* 2024 SMRs,[4] which are considered to have a lower mortality risk than the population of interest (EOS≥300 with uncontrolled COPD). The EAG considers this source to be a plausible option, which allows both the risk of moderate and severe exacerbations to be included and is a consistent source for data used in the model. However, the EAG acknowledges the company's concerns with the uncertainty in using IRRs and SMR that may not be fully reflective of the patient population. In addition, while the EAG considers there to be minimal risk of double-counting the mortality impact of severe exacerbations with the use of a severe exacerbation CFR and SMRs from Whittaker *et al.* 2024,[4] this may not be the case for moderate exacerbations (28% of all patients had moderate exacerbations only). Therefore, it may be more likely that any mortality impact of moderate exacerbations is already accounted for in the SMRs.

Following discussion with a clinical expert, the company provided an addendum to their original response to include an alternative CFR based on two studies published by Echevaria *et al.* based on data between 2008 and 2014.[10, 11] These were both based on six hospitals in England and include COPD patients admitted for severe hospitalisation. Echevaria *et al.* 2017[10] reported all-cause mortality in the 90 days following discharge (i.e. excluding those who died during inpatient stay), while Echevaria *et al.* 2022[11] reported both inpatient mortality and one-year mortality (both with and without inpatient deaths included). From data included in these studies, the company estimated a 90-day case fatality rate.

- Of the 2645 patients included in Echevaria *et al.* 2022,[11] 228 patients died during inpatient stay.
- 2417 patients were reported in Echevaria *et al.* 2017,[10] which appears to be the 2645 patients minus those that died during inpatient stay. Of the 2417 patients, 234 died within 90-days post discharge.
- The company therefore calculate a CFR of severe exacerbation of 17.5% ((228 + 234)/2645). This includes inpatient deaths and post 90-day discharge.

The company notes that this is higher than the NACAP estimate of 11.9%, and proposes it might be due to NACAP data not being spirometry- and physician-confirmed COPD, as was done in the Echevaria *et al.* studies.

The EAG notes the uncertainty regarding the true CFR applicable to the population of interest. While the company noted that the committee accepted a similar figure to Hoogendorn *et al.* of 15.3% in the TA461 for roflumilast,[12] the EAG during the appraisal preferred the NACAP 2014 data and it was stated in the final guidance that *"….[The committee] heard from the clinical expert that it is difficult to be precise about the mortality rate because of variation each year. The committee concluded that the company's estimate was reasonable but also recognised that post-hospitalisation mortality was a key driver of the results*.". The EAG notes that there is the same uncertainty regarding the most appropriate value in the current appraisal. The EAG in TA461 noted that they did not consider the 15.3% from Connolly as the preferred option as it was based on data from before 2006 and audit data from the clinical audit of COPD exacerbations admitted to acute units in England 2014 had shown a continual decrease in the post-hospitalisation mortality rate between 2003 and 2014 (16.3% in 2003, 14.2% in 2008 and 12.0% in 2014).[13, 14]

While the median survival estimates from the economic model using alternative assumptions for the CFR presented by the company are useful, the EAG does not consider it appropriate to try and align the CFR to produce median survival estimates in line with those produced from the analyses of the RWD. As previously noted, these have limitations in the generalisability to the population of interest, particularly as they all had a higher average age than that used in the model, which will impact on median survival.

Based on the NACAP 2018-2020 data being the most recent and representing the largest dataset available to provide an estimate for the CFR of England and Wales (90-day mortality based on 9999

deaths out of 83,994),[6] the EAG considers this to be the most relevant to the appraisal. However, it is acknowledged that there is high uncertainty around the true value and the data provided by the company based on the UK studies by Echevaria *et al*[10, 11], indicate that this could be higher (17.5%). It is noted that these studies used data from 2008 to 2014.

The EAG also notes that for patients who have experienced a severe exacerbation in the current year, the economic model captures the increased probability of future severe exacerbations in the following cycle through the transition probabilities. This is particularly high for patients in the background therapy only arm due to the lifetime treatment effect applied for dupilumab. Therefore, while using the 90-day mortality rate from the NACAP data may risk not capturing longer-term increased risk of mortality from severe exacerbations in that year, patients are at a higher risk of a severe exacerbation in the following model cycle and therefore have the CFR applied again. As discussed in Section 2.1, there is uncertainty in the true effect of dupilumab on severe exacerbations compared to background therapy only and the difference between the two treatment arms in the rate of severe exacerbations; therefore the resulting mortality difference is uncertain.

2.7 Scenario analysis applying a CFR due to exacerbations without the application of SMRs

The company provided the results of a scenario analysis in which COPD mortality is modelled only through the severe exacerbations CFR, i.e. no SMRs based on COPD severity applied. The committee acknowledged that this scenario may be conservative but noted it would be useful for assessing the impact of this assumption on cost-effectiveness estimates. The company provided the ICERs related to this scenario in their response, with the full deterministic cost-effectiveness results reproduced by the EAG below.

Interventions	Total Costs (£)	Total LY	Total QALYs	Δcosts (£)	ΔLYs	Δ QALYs	ICER (£/QALY)
Deterministic results							
Background Therapy	[redacted]	[redacted]	[redacted]	-	-	-	-
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results							
Background Therapy	[redacted]	[redacted]	[redacted]	-	-	-	-
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

The EAG agrees with the committee's acknowledgement that this scenario may be conservative. The company also performed a range of analyses showing the impact on the ICER and median survival estimates from the model when applying CFRs in 5% increments ranging between 40% and 10%, with no SMRs applied. The corresponding probabilistic ICERs ranged from [redacted] to [redacted].

The company also provided a sensitivity analysis in which no SMRs are applied and the CFR of 15.6% is doubled to account for the additional risk of mortality due to moderate exacerbations that were not captured in the scenario analysis to provide an upper limit of the most plausible CFR. The EAG notes that the company used a CFR of 31.6% instead of 31.2% (double 15.6%). A CFR of 31.2% results in a deterministic ICER of [redacted]. As noted by the company, this sensitivity analysis should be treated with caution due to the unknown contribution to the CFR of moderate exacerbations.

An additional scenario was also provided in the company's addendum document in which the one-year mortality rate reported Echevaria *et al.* 2017[10] of 29.8% is applied as a CFR. In this scenario, to avoid double-counting no SMRs are applied. This resulted in a deterministic ICER of [redacted] and a probabilistic ICER of [redacted] (see Table 3 and 4 of company response addendum for full results). This scenario had a median survival of ≈7.17 years in the background therapy only arm.

3 Updated cost-effectiveness results and additional scenarios

The company's response and additional stakeholder submissions have provided the EAG with more clarification regarding the use of a CFR in conjunction with SMRs to model mortality, and as such the updated EAG base-case analysis reflects this. However, there are still a number of uncertainties remaining. The EAG has presented an updated base-case analysis and a range of scenarios around this below.

3.1 Updated EAG base case analysis

Based on committee preferences, the EAG updated their base case analysis to include the multiplier to the FEV_1 decline estimates from Fenwick *et al.*, used to inform transitions between COPD health states. The EAG also updated two further inputs, detailed below, which now account for the only

differences between the company and EAG base case. The results presented in Table 3 include these amendments applied separately:

- As discussed in Section 2.1, the magnitude of the reduction in severe exacerbations is uncertain and the EAG considers the company's modelling approach informing the RRs for severe exacerbations split by COPD severity stage to overestimate the impact of dupilumab on the reduction in severe exacerbations. Therefore, the EAG applies the same RRs calculated from moderate exacerbations to severe exacerbations.
- The EAG considers the NACAP CFR for severe exacerbations (11.9%) to be the most appropriate and applies this in the update base case analysis.[6]

Table 3. EAG preferred amendments (deterministic)

	Results per patient	Dupilumab + background therapy	Background therapy only	Incremental value
0	Company updated base case			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			[redacted]
1	Severe exacerbation RRs equivalent to moderate exacerbation RRs by COPD severity			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			[redacted]
2	CFR of 11.9% from NACAP 2018-2022[6]			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			[redacted]

Abbreviations: CFR, case fatality rate; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; RR, rate ratio.

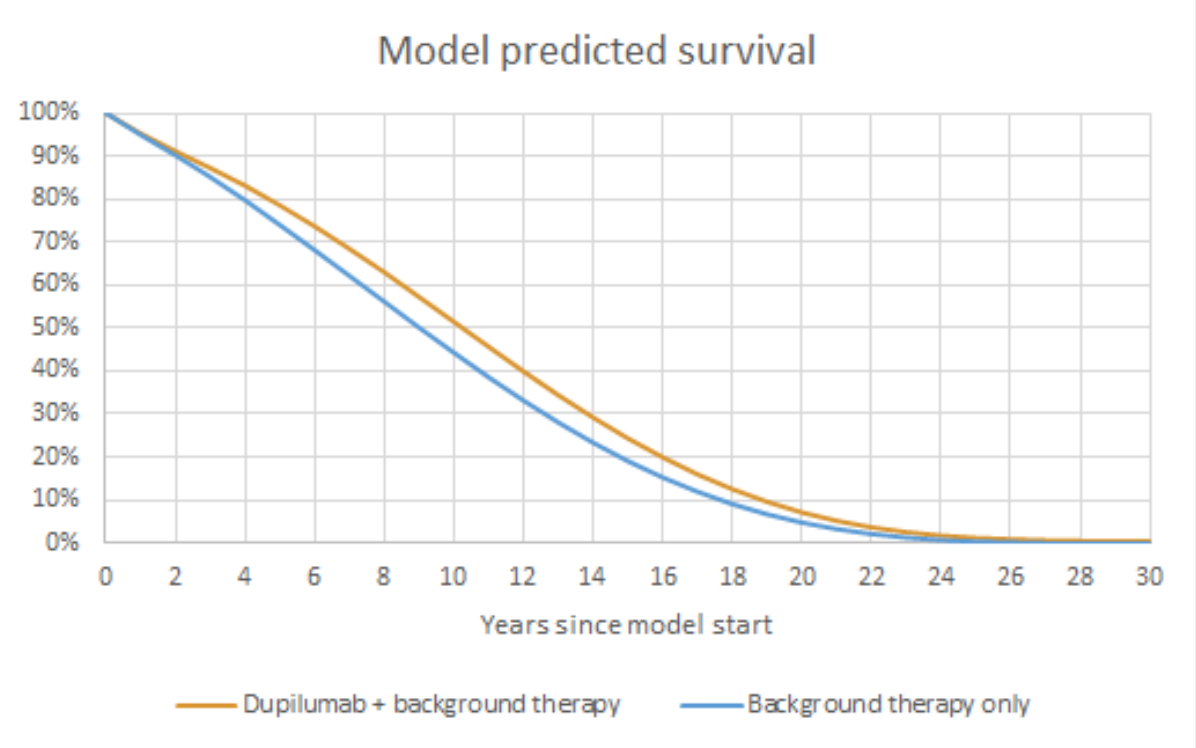
Table 4 presents the results of the EAG updated base case with both amendments applied. The EAG notes that in the EAG updated analysis, the median survival in the background therapy only arm is 9 years, as shown in Figure 2. In the company's updated base-case, median survival in the background therapy only arm was ≈8.3 years.

Table 4. EAG updated base case analysis

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Dupilumab + background therapy	[redacted]	[redacted]	[redacted]	-	-	-	-
Background therapy only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results							
Dupilumab + background therapy	[redacted]	[redacted]	[redacted]	-	-	-	-
Background therapy only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

Figure 2. Model predicted survival in EAG updated base-case analysis



3.2 EAG additional scenario analyses

As previously discussed, there are a number of uncertainties remaining, some of which the EAG was unable to explore further (e.g. continued treatment effect).

The EAG notes that in the RWD presented by the company, the average age of patients was higher than the start age of the model, which is based on the trial data (65). As noted by the company in their response to draft guidance, "*…patient characteristics at baseline for the English and French real world data shown in Table 9, suggest that the average age of patients in the population of interest is around 69 to 70 years old*". Therefore, the EAG has performed an analysis in which the start age of the model is 69 years, as this appears to be more reflective of the UK population of interest and may be the most plausible start age.

As discussed in Section 2.6, there is uncertainty regarding the most appropriate CFR to use in the model. The company provided a range of analyses using alternative sources, found in the company's response to draft guidance. The EAG also presents the use of the higher CFR of 17.5% calculated from the company's additional analysis of Echevaria *et al.* 2017[10] and 2022.[11] The EAG notes the impact of using the CFR of 15.6%, used in the company's base case, is equivalent to Scenario 1 in Table 3.

The EAG also performed an additional scenario analysis in which the RR applied to derive the annual exacerbation rates in the dupilumab arm is based on the primary clinical trial outcome (RR 0.69). In this scenario, the RR does not differ between severe and moderate exacerbations or COPD severity stage. In addition, this is applied all dupilumab patients in the decision tree and all dupilumab responders which informs the Markov model.

In addition, due to the uncertainty on the most appropriate data for estimating the reduction in severe exacerbations, the EAG has also presented the results of a scenario in which the same approach and RRs used in the company base case is applied, but the CFR for mortality is set to 11.9% and model start age is 69.The EAG notes that these analyses are provided deterministically only, shown below in Table 5.

Table 5. Additional sensitivity analyses applied to the updated EAG base-case (deterministic)

	Results per patient	Dupilumab + background therapy	Background therapy only	Incremental value
0	EAG updated base case			

	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			[redacted]
1	Model start age of 69			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			[redacted]
2	CFR of 17.5% based on Echevaria *et al*.			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			[redacted]
3	RR of trial primary outcome (0.69) used to inform all dupilumab exacerbations			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			[redacted]
4	RR for exacerbations modelled as per company base case, CFR of 11.9% and start age 69			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			[redacted]

Abbreviations: CFR, case fatality rate; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; RR, rate ratio.

As shown above, the use of the RR for exacerbations based on the primary trial outcome (0.69), applied across all COPD severity groups, had a minimal impact on the ICER.

The table below presents the model-predicted approximate median survival for each additional scenario presented by the EAG. The median survival for background therapy in scenarios 1 and 4 is equal, as the difference between these scenarios only impacts on the dupilumab arm of the model.

Table 6. Model predicted median survival for EAG additional scenario analyses

EAG additional scenario analyses		Median survival (years)	
		Dupilumab + background therapy	Background therapy only
0	EAG updated base case	10.2	9.0
1	Model start age of 69	8.75	7.8
2	CFR of 17.5% based on Echevaria et al.	9.3	7.95
3	RR of trial primary outcome (0.69) used to inform all dupilumab exacerbations	10.2	9.0

4	RR for exacerbations modelled as per company base case, CFR of 11.9% and start age 69	9.2	7.8

Abbreviations: CFR, case fatality rate; EAG, External Assessment Group; RR, rate ratio.

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Sanofi response following the second Appraisal Committee Meeting (ACM2)

We are grateful to the committee for the opportunity to respond to their request for additional analyses around the relative risk ratios for combined moderate or severe exacerbations following ACM2.

This document responds specifically to the following requests:

- RRs for each COPD GOLD severity category based on the combined moderate and severe exacerbations, split between all patients and responders only.
- Cost effectiveness modelling based on these RRs, and including the committee's other preferred assumptions (notably the latest NRAP CFR %)

We have structured our response in the following way:

1. Brief discussion about the validity of the proposed analysis
2. Relative risk for the combined moderate or severe exacerbations split by GOLD stage and responder status.
3. Cost effectiveness results
4. Conclusions

1. Validity of the proposed analysis.

1.1 Influence of the stopping rule

The stopping rule agreed by the committee, specifically defines responders based primarily on a reduction (or no increase) in severe exacerbations and not necessarily a corresponding reduction in moderate events). It is therefore logical to expect that responders will have a lower severe exacerbation relative risk compared to that for moderate exacerbations. This is by design to ensure that patients not benefiting from treatment do not continue, and that responders are those benefitting from severe exacerbation reduction in particular - the most important clinical aim of treatment. This aim was confirmed by the clinical expert at committee who also supported the fact that responders would be expected to have a lower risk for severe vs. moderate exacerbations.

The separate observed magnitudes for moderate and severe exacerbation RR ratios should remain in place in the model as they do in the Sanofi base case to preserve proper functioning of the stopping rule and make best use of the directly observed data. The separate moderate and severe exacerbation RR ratios are based on pooled BOREAS & NOTUS data, two large phase 3 registrational studies. We acknowledge that the severe event rate in the trials was relatively low and underrepresented in the GOLD 1 and 4 health state categories due to the trial inclusion criteria, but not so low as to preclude robust analyses of the magnitude of relative risk overall (not split by GOLD category), with a statistically significant p value <0.0001 in the responder population.

Despite moderate and severe relative risks generally expected to be similar in magnitude in COPD populations (as in the 'All population'), this is not the case when pre-selecting a sub-population selected for severe exacerbation reduction (as in the Responder population). This means that it is methodologically incorrect to assign a number derived from the combined exacerbation risk to the severe (or moderate) exacerbation RR ratio. This would override the stopping rule criteria, and would misrepresent its output, and furthermore would not reduce uncertainty. It would also cause the modelled payoffs (costs and QALYs) for moderate and severe events to be skewed.

1.2 Brief comparison of the Sanofi base case and the EAG preferred assumptions for relative risk ratios

The Sanofi base case incorporated the directly observed evidence from the pooled data for the BOREAS and NOTUS studies for patients with an opportunity to reach week 52.

There is uncertainty in the RR ratios for the GOLD 1 and 4 health states which arises from the trial inclusion criteria specifying 'moderate or severe' disease (equivalent to GOLD 2 and 3). Therefore, for the purposes of the modelling, we applied conservative estimates. In the 'ALL patients' category we set the RR to 1.00 (equal to standard of care). In the very severe stage for responders there were no events in the dupilumab arm (which would suggest a RR of 0.00), so we set this to be equal to the GOLD 3 category.

In the EAG model the severe RR ratios were set to be the same as that for moderate events. In the responder population in particular it would be an incorrect approach to replace the observed severe exacerbation RR with that for moderate RR dupilumab, for the reasons outlined above.

2. Relative risk for the combined moderate or severe exacerbations split by GOLD stage and responder status.

We understand that an alternative approach to either the company base case or the EAG preference has been requested by the committee to reduce uncertainty perceived in the low severe event numbers. This uses combined moderate or severe RR ratios in place of severe RR ratios.

However, this uncertainty can instead be minimised, while maintaining the integrity of observed trial data and the model-required separation of moderate and severe RRs (especially in the responder population), by pooling the moderate events across GOLD categories and pooling the severe events across GOLD categories. In this way the uncertainties for RRs in GOLD categories 1 and 4 would be addressed, with the legitimate assumption that the RRs should be likely similar across all GOLD categories (this was noted by clinical expert opinion offered at committee that GOLD staging is less relevant to consider once severe exacerbations are underway), and awareness that the model is more heavily driven by RRs in GOLD 2 & 3 due to trial inclusion criteria. Uncertainty in the severe event rate as a whole is also addressed by pooling GOLD categories. The highly significant ($p<0.0001$) responder data for severe exacerbations when pooled across GOLD categories supports this.

However, we understand the committee prefers pooling across moderate or severe exacerbations, as per the primary endpoint in the studies, but maintaining the split by GOLD category and responder status. We do not believe this addresses uncertainty due to small numbers of severe exacerbations in the GOLD 1 and 4 categories and it incorrectly reduces the expected benefit observed for responder patients to the main outcomes of importance in COPD – severe exacerbation reduction (as described in 1.1 above)

Notwithstanding the arguments above we have derived the requested estimates for the annualized moderate or severe exacerbation event rates. The individual annualized rate of moderate or severe exacerbation events in patients with COPD was evaluated, comparing treatment with dupilumab versus SoC. These data are presented in Table 1. The inputs as they appear in the model are presented in Appendix 1.

Table 1. Pooled Annualized moderate or severe exacerbation event rate and Relative Rate ratios.*

Analysis	Annualized moderate or severe exacerbation event rate		Relative risk vs. placebo (95% CI; SE)	p-value
	SoC (95% CI; SE)	Dupilumab (95% CI; SE)		
ALL patients				
GOLD 1	[redacted]	[redacted]	[redacted]	0.466
GOLD 2	[redacted]	[redacted]	[redacted]	<0.001
GOLD 3	[redacted]	[redacted]	[redacted]	0.021
GOLD 4	[redacted]	[redacted]	[redacted]	0.024
Responders				
GOLD 1	[redacted]	[redacted]	[redacted]	0.326
GOLD 2	[redacted]	[redacted]	[redacted]	<0.001
GOLD 3	[redacted]	[redacted]	[redacted]	<0.001
GOLD 4	[redacted]	[redacted]	[redacted]	0.002

*Individual Exacerbation Rate and Relative Risk Analysis based on Bootstrap

The mean exacerbation rate was estimated for each treatment arm, broken down by population (All and Responders) and further stratified by GOLD category, using bootstrap resampling (n = 1000 replicates) to derive robust 95% confidence intervals (CI). (Bootstrap is a non-parametric method that allows empirical estimation of variability without relying on distributional assumptions). This technique is used here in particular, to derive robust CIs and SEs, for use in the probabilistic analysis.

The relative risk (RR) was calculated as the ratio of mean exacerbation rates between the dupilumab and SoC groups. The 95% CI for RR was derived via bootstrap, and the p-value was computed as the proportion of bootstrap RR values greater than or equal to 1. This reflects the clinical hypothesis that dupilumab reduces exacerbation risk (RR < 1), where the threshold of 2.5% aligns with the upper limit of the CI.

3. Cost-effectiveness.

3.1 Updated model settings

The following settings have been used in the updated model to reflect the established committee preferences and the new RR ratios requested. The key changes are presented in Table 2 below.

Table 2 Updated model inputs

Parameter	Updated parameter estimate	Change from original Sanofi base case	Justification
Changes following ACM2			
CFR	14.2%	15.6%. Hoogendorn 2011.	In line with committee preference. Updated CFR taken from the most recent NRAP estimate for 90 day mortality following a severe hospitalised exacerbation.
Relative Risk ratios	• Pooled moderate and severe exacerbations. • Split by GOLD stage and responder status See [Dupilumab Trial inputs (I684:AC6840 and (I698 : AC698)]	Split by moderate and severe exacerbations, GOLD stage and responder status	In line with committee request.
Changes following ACM1			
Adjusted Fenwick risk equation (T2 modifier)	1.52 multiplier. Fenwick FEV1 decline adjusted according to CanCOLD.	No change	Committee preference
Utility	Derived from the utility regression model including only statistically significant covariates.	Change from treatment specific utilities	Committee preference
Baseline distribution of COPD severity at start of Markov	Trial baseline distribution for SoC with trial treatment effect to inform dupilumab distribution	Change from ITT trial data at end of trials (removal of the FEV1 trial effect)	Committee preference
Non-fatal CV events	No difference between arms	Change from different rates between arms	Committee preference
% requiring nurse home administration	5%	Change from 0%	Committee preference
Follow-up appointment after severe exacerbation	37% within 90 days	Change from 17% at 30 days and 37% at 90 days	Committee preference

3.2 Updated cost effectiveness results

The probabilistic and deterministic results derived from the updated model are presented in Table 3 and Table 4.

Table 3. Updated model results: Probabilistic

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Background Therapy	[redacted]	[redacted]	[redacted]				

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Table 4. Updated model results: Deterministic

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Background Therapy	[redacted]	[redacted]	[redacted]				

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

The scatter plot and cost-effectiveness acceptability curve (CEAC) are presented in Figure 1 and Figure 2, respectively.

Figure 1. Scatter plot for incremental cost-effectiveness results (1,000 iterations)

[redacted]

PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 2. Cost-effectiveness acceptability curve (1,000 iterations

[redacted]

Summaries of the disaggregate results are presented in Appendix 2.

4. Conclusion.

We have discussed the methodological issues common to all the approaches that replace observed severe exacerbation rate ratios with other exacerbation measures. And whilst we are concerned with the methodological and logical shortcomings of such approaches preferred by the committee, we have provided the additional requested analysis. This includes the combined moderate or severe exacerbation RR ratios for each GOLD category, for 'ALL' and 'Responder' populations. The analysis presented here also uses the value for CFR, according to the latest NRAP estimate for 90-day mortality following a severe exacerbation.

The probabilistic ICER using the updated RR ratios and CFR is [redacted] / QALY. This is [redacted] / QALY [redacted] than the company base case post ACM1 (probabilistic ICER = [redacted] / QALY, which included the analyses preferred by the committee following ACM1 (See Table 2).

Appendix 1. RR inputs as they appear in the model.

Rate Ratio inputs	Responders		All patients		Responders		All patients	
Gold Stage	Moderate exacerbation (RR vs Background Therapy)	Severe exacerbation (RR vs Background Therapy)	Moderate exacerbation (RR vs Background Therapy)	Severe exacerbation (RR vs Background Therapy)	Moderate exacerbation (RR vs Background Therapy)	Severe exacerbation (RR vs Background Therapy)	Moderate exacerbation (RR vs Background Therapy)	Severe exacerbation (RR vs Background Therapy)
	Mean value				Standard Error			
1: Mild COPD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2: Moderate COPD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3: Severe COPD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4: Very Severe COPD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Appendix 2. Disaggregated results.

Table 5. Summary of disaggregated results (LYs)

Outcomes	Dupilumab + Background Therapy	Background Therapy
LYs - Mild COPD	[redacted]	[redacted]
No exacerbation	[redacted]	[redacted]
Moderate exacerbation	[redacted]	[redacted]
Severe exacerbation	[redacted]	[redacted]
LYs - Moderate COPD	[redacted]	[redacted]
No exacerbation	[redacted]	[redacted]
Moderate exacerbation	[redacted]	[redacted]
Severe exacerbation	[redacted]	[redacted]
LYs - Severe COPD	[redacted]	[redacted]
No exacerbation	[redacted]	[redacted]
Moderate exacerbation	[redacted]	[redacted]
Severe exacerbation	[redacted]	[redacted]
LYs - Very severe COPD	[redacted]	[redacted]
No exacerbation	[redacted]	[redacted]
Moderate exacerbation	[redacted]	[redacted]
Severe exacerbation	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]

COPD = chronic obstructive pulmonary disease; LY = life year

Table 6. Summary of disaggregated results (QALYs)

Outcomes	Dupilumab + Background Therapy	Background Therapy
QALYs - Mild COPD	[redacted]	[redacted]
No exacerbation	[redacted]	[redacted]
Moderate exacerbation	[redacted]	[redacted]
Severe exacerbation	[redacted]	[redacted]
QALYs - Moderate COPD	[redacted]	[redacted]
No exacerbation	[redacted]	[redacted]
Moderate exacerbation	[redacted]	[redacted]
Severe exacerbation	[redacted]	[redacted]

Outcomes	Dupilumab + Background Therapy	Background Therapy
QALYs - Severe COPD	[redacted]	[redacted]
No exacerbation	[redacted]	[redacted]
Moderate exacerbation	[redacted]	[redacted]
Severe exacerbation	[redacted]	[redacted]
QALYs - Very severe COPD	[redacted]	[redacted]
No exacerbation	[redacted]	[redacted]
Moderate exacerbation	[redacted]	[redacted]
Severe exacerbation	[redacted]	[redacted]
CV event utility decrement	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]

COPD = chronic obstructive pulmonary disease; QALY = quality-adjusted life year

Table 7. Summary of disaggregated results (costs)

Outcomes	Dupilumab + Background Therapy	Background Therapy
Drug acquisition costs	[redacted]	[redacted]
Drug administration costs	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]
Exacerbation management	[redacted]	[redacted]
COPD management	[redacted]	[redacted]
CV event costs	[redacted]	[redacted]
Total costs	[redacted]	[redacted]

COPD = chronic obstructive pulmonary disease; CV = cardiovascular

Table 8. Summary of disaggregated results (health outcomes)

Outcomes	Dupilumab + Background Therapy	Background Therapy
Number of exacerbations	[redacted]	[redacted]
Moderate exacerbation	[redacted]	[redacted]
Severe exacerbation	[redacted]	[redacted]
Number of deaths	[redacted]	[redacted]
Deaths in mild COPD	[redacted]	[redacted]
Deaths in moderate COPD	[redacted]	[redacted]

Outcomes	Dupilumab + Background Therapy	Background Therapy
Deaths in severe COPD	[redacted]	[redacted]
Deaths in very severe COPD	[redacted]	[redacted]
Deaths in no exacerbation	[redacted]	[redacted]
Deaths in moderate exacerbation	[redacted]	[redacted]
Deaths in severe exacerbation	[redacted]	[redacted]
Number of responders	[redacted]	[redacted]
CVD associated outcomes	[redacted]	[redacted]
Time on treatment (years)	[redacted]	[redacted]
Time off treatment (years)	[redacted]	[redacted]

COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease

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

EAG review of updated analysis following ACM2

September 2025

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1 EAG review

1.1.1 *Updated case fatality rate for severe exacerbations*

Based on the NACAP 2018-2020 data being the most recent and largest dataset available to provide an estimate for the case fatality rate (CFR) in England and Wales at the time of ACM2, the EAG considered this to be the most relevant for this appraisal. Access to the latest data is highly relevant and applicable. However, due to the time frame of the most recent report and the lack of further information currently available, it is unclear whether the latest NRAP estimate may be confounded by the COVID-19 pandemic and any influence this may have had on the resulting mortality estimates. The EAG notes that previous clinical audit reports had been showing a continual decrease in the post-hospitalisation mortality rate since 2003 and, therefore, it is unclear if the recent increase (11.9% in 2018-20 to 14.2% in 2021-23) may be related to COVID-19. However, without further details, the EAG is unable to comment further.

The updated EAG base-case ICER with a 14.2% mortality figure applied is [redacted].

1.1.2 *Updated risk ratios for exacerbation rates*

Following ACM1, the EAG updated its base-case analysis to inform the relative risk ratios (RRs) for exacerbations applied in the economic model by applying the rate ratios derived from moderate exacerbations for each COPD severity to severe exacerbations. It was noted in the EAG response to draft guidance that the EAG's preference would have been to apply RRs for each COPD severity based on the combined moderate and severe exacerbations, split between all dupilumab patients and responders only. This was due to the combined moderate and severe exacerbations being the primary trial outcome, a lack of statistically significant differences in severe exacerbations identified and small patient numbers informing severe exacerbation rates when split by GOLD stage. In addition, it was noted by clinical experts at ACM1 that the mechanism for moderate and severe exacerbations is broadly similar and the rate reduction would be expected to be similar.

The company has provided the requested RRs in response to a request from committee following ACM2. The company states that the uncertainty in the severe exacerbation rates can be addressed by pooling across GOLD stage and notes a "highly significant difference" for responders when using this approach. The EAG assume the company is referring to the modified intention to treat (mITT) analyses presented as part of the response to draft guidance, which as previously noted by the EAG,

are *post-hoc* analyses which break randomisation, no longer reflect the full ITT population and can overestimate the treatment effect. At best, they more closely represent a per-protocol analysis.

All updated results numerically favour dupilumab over standard of care, with statistically significant benefits of dupilumab seen in GOLD stages 1, 2 and 3 in both the responder and all patient analyses.

The EAG notes that in the estimation of the RRs for combined moderate and severe exacerbations, the company used the individual annualised mean event rate, whereas all previously calculated RRs used in the model by the company had been estimated using the unadjusted annualised event rate. The EAG notes that using the individualised mean approach results in more favourable RRs for dupilumab compared to placebo than using the unadjusted annualised event rate.

The company did not provide any justification as to why they had changed their approach to calculating the RRs. The combined rate for moderate and severe exacerbations appears to be simply adding the individual annualised mean rate for moderate exacerbations and the individual annualised mean rate for severe exacerbations together (Table 1 and Table 2). It is unclear to the EAG how the individual annualised rates have been calculated. However, the EAG notes that combining mean rates will result in a loss of information compared to using the raw trial data and any estimation of uncertainty that the company has undertaken around the combined mean is likely to be less accurate and underestimate the true uncertainty of the combined outcome compared to using the unadjusted approach (see below).

The EAG notes that the previously used approach (unadjusted annualised rate) is in line with the directly observed trial data as it is calculated based on the observed total number of moderate or severe events divided by the total patient-years, to provide an annualised event rate. The EAG notes that this is the primary outcome from the BOREAS and NOTUS trials. Therefore, the EAG considers that this is the most appropriate method that should have been used in any updated analyses, as was previously applied by the company. In addition, by using an alternative method to derive RRs, the company's results are not comparable with those previously presented.

On further inspection, the EAG identified the values required to calculate the RRs for the combined moderate and severe exacerbations and has presented these in Table 1 (all patients) and Table 2 (responders only), with a summary of the resulting RRs in Table 3.

Table 1. Data on moderate and severe events used to derive rate ratios (RRs) using company original approach and updated **(all patients)**. Data taken from Table 1.34.1 of Sanofi - summary of *post-hoc* analyses for Markov cost-effectiveness (CE) model

All patients	Gold Grade 1		Gold Grade 2		Gold Grade 3		Gold Grade 4	
	Placebo	Dupilumab	Placebo	Dupilumab	Placebo	Dupilumab	Placebo	Dupilumab
Company's original approach								
Total number of moderate exacerbation events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of severe exacerbation events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of moderate or severe exacerbation events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total patient-years followed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unadjusted annualised moderate or severe exacerbation event rate (total number of moderate and severe events/total patient-years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resulting RR (Dupilumab annualised rate/placebo annualised rate)		[redacted]		[redacted]		[redacted]		[redacted]
Company's updated approach								
Individual annualised moderate exacerbation event rate, mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Individual annualised severe exacerbation event rate, mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Individual annualised moderate or severe exacerbation event rate, mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resulting RR (Dupilumab annualised rate/placebo annualised rate)		[redacted]		[redacted]		[redacted]		[redacted]

Table 2. Data on moderate and severe events used to derive rate ratios (RRs) using company original approach and updated (**responders only**). Data taken from Table 1.35.1 of Sanofi - summary of *post-hoc* analyses for Markov cost-effectiveness (CE) model

Responder only	Gold Grade 1		Gold Grade 2		Gold Grade 3		Gold Grade 4	
	Placebo	Dupilumab	Placebo	Dupilumab	Placebo	Dupilumab	Placebo	Dupilumab
Company's original approach								
Total number of moderate exacerbation events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of severe exacerbation events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of moderate or severe exacerbation events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total patient-years followed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unadjusted annualised moderate or severe exacerbation event rate (total number of moderate and severe events/total patient-years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resulting RR (Dupilumab annualised rate/placebo annualised rate)		[redacted]		[redacted]		[redacted]		[redacted]
Company's updated approach								
Individual annualised moderate exacerbation event rate, mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Individual annualised severe exacerbation event rate, mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Individual annualised moderate or severe exacerbation event rate, mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resulting RR (Dupilumab annualised rate/placebo annualised rate)		[redacted]		[redacted]		[redacted]		[redacted]

Table 3. Calculated rate ratios (RRs) for combined moderate and severe exacerbations using different approaches for estimation

Calculated RRs for combined moderate and severe exacerbations	Company approach - individual annualised moderate or severe exacerbation event rate (mean)	EAG preference - Unadjusted annualised moderate or severe exacerbation event rate
All patients		
GOLD 1	[redacted]	[redacted]
GOLD 2	[redacted]	[redacted]
GOLD 3	[redacted]	[redacted]
GOLD 4	[redacted]	[redacted]
Responders only		
GOLD 1	[redacted]	[redacted]
GOLD 2	[redacted]	[redacted]
GOLD 3	[redacted]	[redacted]
GOLD 4	[redacted]	[redacted]

The EAG has provided an updated ICER using the RRs derived using the unadjusted annualised moderate or severe event rates (Table 4). This ICER also includes the updated CFR for severe exacerbations from NRAP data. Due to time constraints, the EAG notes that they were unable to produce updated standard errors associated with the RRs and, therefore, have provided results deterministically only. However, the EAG notes that the deterministic and probabilistic results were previously found to be largely similar.

Table 4. Deterministic results applying committee preferences and EAG preferred approach for deriving RRs

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Dupilumab + background therapy	[redacted]	[redacted]	[redacted]	-	-	-	-
Background therapy only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

Sanofi response to the EAG analyses following the second Appraisal Committee Meeting (ACM2)

We are grateful to the committee for the opportunity to respond to the EAG comments on the Sanofi additional analyses provided following ACM2.

This document responds specifically to the following:

- Discussion of the relative merits of the committee-preferred approach.
- Justification for the use of the updated individualised / bootstrapping methodology to calculate RRs for each COPD severity stage, based on the committee-preferred approach to use the combined moderate OR severe exacerbation outcome, applied to the 'all patients' and 'responder' populations.
- Update to the EAG modelling to include probabilistic analysis

We have structured our response in the following way:

1. Executive summary
2. Choice of the appropriate endpoint for exacerbation reduction in the model.
3. Implementation of the moderate OR severe exacerbation reduction combined endpoint.
    a. Justification for the alternative approach to calculating the Relative Rate Ratios Cost effectiveness results
    b. Exacerbation rates for Moderate OR severe exacerbations by GOLD stage
    c. Generation of measures of variance around the RRRs for these rates.
4. Cost-effectiveness results.
5. Conclusions

1. Executive summary

There are two important issues that remain in this appraisal.

1. Which data to use to describe exacerbation benefit.
2. The methodology used to calculate the event rates, relative risk ratios and standard errors around these.

1. Choice of exacerbation data

The differences in the company and committee-preferred approaches to the use of the exacerbation data used for the calculation of relative risks are summarised below. (This terminology will be used throughout the document for clarity).

- **Company-preferred approach – maintain separation between moderate and severe exacerbations**. To utilise the directly observed data in BOREAS & NOTUS to calculate RRs, separately for moderate exacerbations and severe exacerbations, and separately for each health state (GOLD severities 1-4)
- **Committee-preferred approach – combine moderate OR severe exacerbations.** To combine moderate and severe exacerbations but maintain separation between GOLD

severity stages. The moderate OR severe exacerbation RRs are used as proxy for the individual moderate exacerbation and severe exacerbation RRs used in the model.

The Committee preference for using combined moderate OR severe exacerbation relative risk (RR) ratios separately by GOLD stage (committee-preferred approach) chooses to ignore the directly available phase 3 trial data for moderate exacerbations and severe exacerbations which is statistically significant in the GOLD 2 and 3 stages and instead uses the RRs for moderate OR severe exacerbations as proxy for these measures.

It assumes dupilumab reduces moderate and severe exacerbations equally. This assumption may hold for the 'All Patients' group but not for 'Responders', who are selected primarily according to the stopping rule based on severe exacerbation reduction. The clinical experts at ACM2 and the trial data confirm responders show greater reduction in severe exacerbations compared to moderate exacerbations. Applying the committee's method undermines the responder criteria and introduces a serious flaw, ultimately undervaluing dupilumab's clinically meaningful and economically relevant benefits.

2. Calculation of the event rates, relative risk ratios and standard errors

It is critical to ensure the event rates, relative risk ratios and the associated measures of variance are derived appropriately with proper consideration of the underlying data. The company and the EAG have differing views on how these relative rates should best be calculated.

The EAG prefers to use an 'unadjusted' methodology which does not take account of the structure of the data. Unadjusted methodology was utilised in the original company submission, but we revisited the validity of this for our response to the committee request for updated exacerbation modelling, to ensure the estimates for the RR ratios are as robust as possible.

Therefore, to better handle uncertainty arising from small sample sizes and high zero counts, we've replaced the original crude unadjusted analysis with a more robust statistical approach. This examines 'individualised' data in which the mean is calculated for all individual patients, followed by bootstrapping to describe variation across each cohort. Contrary to the EAG view that this methodology would lose information, it does in fact use more of the available data than the crude unadjusted analysis, including individual patient time on treatment, to produce more accurate and credible RR estimates and confidence intervals.

We chose the individualised method because unadjusted estimates are likely to be biased—especially in GOLD 1 and 4 stages where patient numbers and event rates are low, and many patients had no events. To demonstrate this, we provided a patient-level analysis showing how the committee's preferred unadjusted method misrepresents the true RR.

The unadjusted method calculates rates and relative rate (RR) ratios by dividing total exacerbations by total patient-years, then compares the SoC and dupilumab arms. However, this approach is crude ignoring individual patient outcomes and distributions. Unadjusted methodology can't directly provide 95% confidence intervals (95%CI) or standard errors (SE). Our updated method using 'individualised' means, accounts for data variability, producing more robust RR estimates and using bootstrapping produces SEs that better reflect the structure of the underlying data.

The preference of the EAG to keep the unadjusted approach seems predicated on nothing more than the fact that this was the original method, and that the alternative 'individualised' methodology appears to favour dupilumab. Neither of which are legitimate reasons to reject it.

The probabilistic ICER using the 'individualised' approach is [redacted] and represents a more credible valuation of dupilumab than the committee-preferred 'unadjusted' approach (probabilistic ICER = [redacted]) which gives no fair recognition to the severe exacerbation data and disregards the distribution of events.

2. Choice of the appropriate endpoint for exacerbation reduction in the model.

The committee preference to use combined moderate OR severe exacerbations as proxy for the individual moderate exacerbation and severe exacerbation RR ratios in the model is flawed.

COPD trials are almost always powered on combined moderate OR severe events since severe exacerbations alone are relatively infrequent events, despite being a key outcome for patients, their clinicians and health-care systems. The primary trial outcome measure of moderate OR severe exacerbations is accepted by regulatory authorities, where there is an assumption that a treatment that results in exacerbation benefit would imply a benefit to moderate exacerbations and severe exacerbation separately. However, this combined outcome is not compatible with accurate and appropriate economic modelling. Indeed, published COPD economic models utilise moderate exacerbation rates and severe exacerbation rates separately since severe exacerbation events cause significantly more detriment to quality of life, treatment costs and mortality, and are predictive of further exacerbation events, and should therefore be properly represented in the modelling.

This is most appropriately achieved using the clinical trial data for moderate exacerbations and severe exacerbations separately. Such outcome data exists as pre-specified analyses for the BOREAS & NOTUS studies. These might not be primary outcome data, but the health economic model requires all outcomes to be split between health states (GOLD severity stages 1-4), to derive costs and QALYs, necessitating the use of post-hoc analyses throughout regardless. The committee-preferred approach ignores the available directly observed phase 3 trial data for moderate exacerbations and severe exacerbations and instead uses the combined RRs for moderate OR severe exacerbations as proxy for these measures.

The underlying assumption that dupilumab would reduce moderate exacerbations and severe exacerbations similarly, has some merit when applied in order to reduce uncertainty, but ONLY if applied to the 'All Patients' population. We strongly object to the application of this approach to the 'Responder' population, where the similarity of moderate exacerbation and severe exacerbation rate reductions no longer holds true. Responders in the model are a population which has been selected primarily on achieving a severe exacerbation reduction. The clinical aim of the responder criteria was supported by clinical expert opinion in ACM2, where it was also confirmed that responders would be expected to have a severe exacerbation reduction greater in magnitude to that for moderate exacerbations. This is what is observed in the BOREAS & NOTUS data filtered by the responder criteria. The responder criteria are designed to ensure that patients who continue dupilumab (in the model, as per real world) have achieved the primary clinical aim of a lower or stable severe exacerbation rate. Applying the committee-preferred approach to the responder population will result in the modelled payoffs for moderate

and severe events (costs and QALYs) to not accurately represent the expected real-world impact.

In contrast, the directly observed data for exacerbation RR in the responder population (company-preferred approach), allows proper functioning of the responder criteria, and results in statistically significant p-values for both the moderate exacerbation RR and severe exacerbation RR in the responder population, with corresponding low uncertainty. This methodology, as originally submitted, should stay in place as it constitutes a more appropriate approach for appropriate health economic modelling and decision making.

The Committee-preferred approach undervalues dupilumab by diluting the clinically meaningful (and statistically significant) severe exacerbation benefits that define treatment responders and drive important real-world clinical and economic outcomes.

3. Implementation of the moderate OR severe exacerbation reduction combined endpoint (Committee preferred assumptions).

Notwithstanding the arguments above, we have provided the requested analysis combining moderate OR severe exacerbations. Recognising the remaining uncertainty inherent in the small sample sizes with a high proportion of patients having no exacerbations, we have applied a more statistically rigorous statistical analysis than the original crude unadjusted methodology. This is discussed below.

3.1. Justification for the alternative statistical approach to calculating the Relative Rate Ratios.

The original submission used the crude unadjusted approach which simply divides the total number of moderate and severe exacerbations by the total patient-years and then calculates the ratio between the SoC and dupilumab arms to derive the RR ratio. We revisited the validity of this methodology for our response to the committee request for updated exacerbation modelling to ensure the estimates for the RR ratios are as robust as possible.

The EAG have stated that the unadjusted method to calculate the event rates uses all the raw data and they favour this approach, this is not the case as we discuss below but there are several other failings associated with this methodology. These are particularly evident when applied to the GOLD 1 and 4 severity states where patient and event rates are low, but also more generally across all health states, where there is strong reason to believe that simple crude unadjusted estimates will be unstable or biased due to the underlying structure of the data.

This becomes particularly apparent when considering the RRs derived from some of the smaller cohorts using the unadjusted approach (See Table 7). For example, it is not credible that the RR ratio for the 'ALL patients' cohort in GOLD 1 would be [redacted], suggesting that dupilumab would result in an approximately [redacted] in exacerbation rate compared to placebo rather than a decrease. This is contrary to the results for the larger cohorts, as well as that seen in the broader ITT population.

Low patient numbers

In the requested analyses the patient numbers are low for the GOLD 1 and 4 stages meaning estimates for rates and relative rates derived from the unadjusted numbers is particularly prone

to error. This error is compounded because no account is taken of variability in individual patient outcomes in the unadjusted analysis.

Low number of events

Small event numbers mean that the underlying distributions are unknown or highly uncertain. This is important because the measure of variance around the key outcome of the RR ratio drives the probabilistic ICER, which is NICEs preferred outcome.

High zero inflation

There are high numbers of patients with no events at all. The mode for moderate OR severe events across all GOLD severity states is 0 and the median event rate is 0 for GOLD 1 to 3. This can clearly be seen in the histograms shown in Appendix A where the first column representing 0 events dominates the other data in each case.

Measures of variance.

The unadjusted methodology cannot be used to calculate measures of variance directly. To mitigate this in our original submission we estimated the variance by using 95% CIs from a model with only treatment as covariate and normally approximated SEs. This requires strong assumptions, and such a model is likely biased due to the structure of the underlying data. We strongly encourage the committee to reconsider how 95%CIs and SEs are calculated and have chosen to use a bootstrapping approach in our updated analysis. This is described below.

Data relevant to the section above is presented in Table 1 below.

Table 1. Patient numbers, proportion with no events or the mean event rates by treatment and GOLD stage.

	GOLD 1		GOLD 2		GOLD 3		GOLD 4	
	SoC	Dup	SoC	Dup	SoC	Dup	SoC	Dup
Number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients with no events (ALL patients)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion with no events (%) (ALL patients)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Therefore, in approaching the new committee-preferred analyses (utilising combined moderate OR severe exacerbations by GOLD stage) we revisited the methodology to find a better method to provide more certainty around the exacerbation means, the RR ratios, and the associated measures of variance.

There were two phases to generating the new data we used in the model:

1. Calculation of robust exacerbation rates for moderate OR severe exacerbations by GOLD stage using an 'individualised' approach.
2. Generation of measures of variance around the RR ratios for these rates using bootstrapping.

Taking each of these in turn...

3.2. Exacerbation rates for Moderate OR severe exacerbations by GOLD stage

The unadjusted method favoured by the EAG methodology ignores variability between individual patients, where event number and time on treatment for individual patients is not considered. This becomes particularly important in small datasets where individual patient variability can drive outcomes, but these patients should not be considered outliers.

The EAG have noted that using the individualised mean approach results in more favourable RR ratios for dupilumab compared to placebo than using the unadjusted annualised event rate. This is true but it provides a more accurate representation of the observed outcomes as described below.

To understand why the individualised mean better presents the data and to answer the concerns of the EAG above, we provide an example below involving patient-level detail for the two calculation methodologies. This compares the individualised mean versus the unadjusted mean for GOLD stage 1 where this effect is most pronounced.

The largest difference between the individualised and unadjusted relative rate means are seen in the GOLD stage 1 'ALL patients' calculations, and so this dataset is used for illustrative purposes. For all other datasets the same principles apply but the differences are smaller due to higher patient numbers and event rates where instability and bias may not be so apparent.

Table 2 provides a description of moderate OR severe COPD exacerbations during the on-treatment period from Week 2 to end of trial (EOT) in the GOLD 1 cohort (assessed at Week 2) for the 'All patients' population.

There were [redacted] patients in the SoC arm and [redacted] in the dupilumab arm. Of these patients only [redacted] and [redacted] had a moderate OR severe exacerbation respectively. The total number of years followed was [redacted] for SoC and [redacted] for dupilumab treated patients.

Table 2 Description of moderate or severe COPD exacerbations during on-treatment period from Week 2 to EOT according to Gold Severity at Week 2 for GOLD stage 1, ALL patients regardless of response.

	SoC (n= 34)	Dupilumab (n=58)
Number of participants with >=1 moderate or severe exacerbation event		
No (%)	[redacted]	[redacted]
Yes (%)	[redacted]	[redacted]
Total patient-years followed (years)	[redacted]	[redacted]
Number of moderate or severe exacerbation events (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
≥4	[redacted]	[redacted]
Total number of moderate or severe exacerbation events	[redacted]	[redacted]

The EAG have criticised the 'individualised' methodology on the basis that it discards data. This is not the case; in fact, it makes more complete use of the data than the unadjusted approach. This is because it considers the event number and time on treatment for each patient individually. This is very important in the smaller datasets where individual patient's events may count more towards the overall results, considering the high number of patients without events (0's). The full dataset is shown below in Table 3 for SoC and in Table 4 for dupilumab treated patients.

Table 3 Individual patient level data for GOLD 1 – SoC cohort, by number of exacerbation events (moderate OR severe) and time on treatment, with unadjusted and individualised methods.

Dummy patient number	Number of events	Actual days on treatment	Overall average days on treatment per patient (total days / total patient number)	**Unadjusted mean (Annualised)**	**Individualised mean (Annualised)**
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
31	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
33	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean Relative Risk				[redacted]	[redacted]

Table 4 Individual patient level data for GOLD 1 – Dupilumab cohort, by number of exacerbation events (moderate OR severe) and time on treatment, with unadjusted and individualised methods.

Dummy patient number	Number of events	Actual days on treatment	Overall average days on treatment per patient (total days / total patient number)	**Unadjusted mean (Annualised)**	**Individualised mean (Annualised)**
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
31	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
33	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
35	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
37	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
38	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
39	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
41	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
43	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
46	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
47	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
51	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
53	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
55	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
56	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
57	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
58	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean Relative Risk				[redacted]	[redacted]

The individualised mean is the average of all the individual patient rates (including the 0's). The concerns of the EAG arise from the difference in the results for the SoC arm ([redacted]) being larger than for the dupilumab arm ([redacted]). When the individualised rates are combined in RR ratios the resulting RR ratios are therefore lower than for the unadjusted approach. However, the individualised methodology now more properly reflects the variability in the datasets, which is not accounted for using the unadjusted approach, and results in more accurate mean relative rates.

Inspection of the data in tables 3 and 4 reveals two critical aspects of the data that must be considered.

1. The unadjusted approach effectively assumes that all patients have the same time on treatment, based on the average across the whole cohort. In essence this means that each patient contributes the number of exacerbations divided by the average time on treatment to the mean. (The 'unadjusted annualised event rate'). This is contrary to the directly observed evidence where one of the exacerbating patients in the SoC arm (Table 3, Patient 2, shaded orange) stayed on treatment for only [redacted] days. That patient had an annualised exacerbation rate of [redacted]. This is the 'true' RR for this patient. Conversely, the unadjusted approach assumes that this patient stayed on treatment for the average time (total time on treatment / number of patients: [redacted] years) and therefore the contribution from that one exacerbation in that patient is calculated as [redacted] exacerbations per year. This is NOT the true RR for this patient, and underrepresents the actual data. In the dupilumab arm this differential effect overall is not so pronounced because there are more patients (each individualised mean has less weight than in the SoC arm) and the individualised means are closer to the 'unadjusted annualised event rates', although Patient 5 (shaded orange in table 4) would also be incorrectly accounted for with unadjusted methodology.

2. The example shown here is the most extreme case within the dataset and is used to transparently illustrate the importance of considering all the data including time on treatment. In the datasets which include more events and fewer non-exacerbating patients the effect noted above is not as extreme. In these cases, the unadjusted and individualised methodologies are in more agreement. However, for the purposes of the analyses requested here which include small data sets (GOLD 1 and 4), the individualised methodology provides a more accurate representation of rates generally, and should be used in preference to unadjusted, to calculate RRs for all cohorts (GOLD 1 to 4).

The EAG have suggested that we have calculated the combined rate for moderate and severe exacerbations by simply adding the individual annualised mean rate for moderate exacerbations and the individual annualised mean rate for severe exacerbations together and that this leads to a loss of information. This is not the case. The calculation of the mean for the moderate OR severe exacerbations was carried out for each patient in one step using the entire dataset, as is illustrated above in Table 3 and Table 4 for GOLD stage 1. Whilst it may appear that the individualised means are added up this is simply because mathematically this is the outcome when the means are expressed for moderate exacerbations and severe exacerbations separately. We would like to reassure the committee that the overall mean is calculated from the raw data for each patient and so information is not lost as suggested by the EAG.

3.3. Generation of measures of variance around the RR ratios for these rates.

It is critical to generate robust measures of variance with a high degree of confidence for the RR ratio for the event rates comparing SoC with dupilumab treatment for the economic model as these estimates drive the probabilistic ICER.

It is not true as claimed by the EAG that the estimation of uncertainty developed around the combined individualised means using a bootstrapping technique is less accurate and underestimates the true uncertainty of the combined outcome compared to using the unadjusted approach. Under the original unadjusted methodology, the 95% Cls could not be derived directly so a model had to be developed with a strong assumption of normally approximated SEs to generate measures of variance. (Note we have applied this to the EAG preferred RR ratios to generate the probabilistic analysis which they were unable to provide. See Table 7 below).

We have chosen to use the bootstrapping methodology to develop the required measures of variance directly from the individualised means. Bootstrap is a non-parametric method that allows empirical estimation of variability without relying on distributional assumptions. This is important as the smaller datasets, low event rates and high proportion of patients with no events, (in particular for the severe exacerbation outcome), means that an assumption of normality for underlying distributions cannot be made.

For the bootstrap analysis 1000 samples were drawn at random (resampled with replacement) from the individualised moderate OR severe exacerbation rates. For each sample the mean of the individualised moderate OR severe exacerbation rates for SoC and dupilumab and the RR ratios were then calculated by GOLD stage.

The mean and SE for all RR ratios was then calculated from the 1000 iterations and used in the model for each GOLD stage. This methodology means that there is no need for assumptions around distributions and all the data is used directly.

This approach addresses uncertainty in as robust a way as is possible given the limitations of the dataset.

The individualised event rates are more variable for SoC than dupilumab, demonstrating the more consistent response to treatment for dupilumab treated patients. This is evident in the difference in the Standard Errors (SE) derived for the individualised event rates in each GOLD stage for SoC and Dupilumab patients. (See *Table 5*).

Table 5. SE's for the mean event rates by treatment and GOLD stage for ALL patients and responders.

	GOLD 1		GOLD 2		GOLD 3		GOLD 4	
	SoC	Dup	SoC	Dup	SoC	Dup	SoC	Dup
Individualized SE (ALL patients)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Individualized SE (Responder)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The RR ratios and associated measures of variance calculated using the bootstrapping methodology are presented in Table 6 overleaf.

Table 6. Pooled Annualized moderate or severe exacerbation event rate and Relative Rate ratios.*

Analysis	Annualized moderate or severe exacerbation event rate		Relative risk vs. placebo (95% CI; SE)	p-value
	SoC (95% CI; SE)	Dupilumab (95% CI; SE)		
ALL patients				
GOLD 1	[redacted]	[redacted]	[redacted]	0.466
GOLD 2	[redacted]	[redacted]	[redacted]	<0.001
GOLD 3	[redacted]	[redacted]	[redacted]	0.021
GOLD 4	[redacted]	[redacted]	[redacted]	0.024
Responders				
GOLD 1	[redacted]	[redacted]	[redacted]	0.326
GOLD 2	[redacted]	[redacted]	[redacted]	<0.001
GOLD 3	[redacted]	[redacted]	[redacted]	<0.001
GOLD 4	[redacted]	[redacted]	[redacted]	0.002

*Individual Exacerbation Rate and Relative Risk Analysis based on Bootstrap

The EAG have noted that the individualised approach used to derive RR ratios means that the results are not comparable with those previously presented. However, the Committee-preferred analyses are also not comparable with the previously presented results as they use a proxy for both moderate exacerbations and severe exacerbations.

4. Cost-effectiveness results.

The EAG have provided only the deterministic analysis using their approach. We have updated the 'unadjusted' model to include 95%CIs and the SEs required to perform the probabilistic

analysis using the same methodology we employed in our original submission whereby a negative binomial model with treatment as a covariate was developed with an underlying assumption of normally distributed SEs.

The updated EAG model inputs are presented below in Table 7.

Table 7 EAG preferred RR ratios with associated 95%CI and SEs.

All patients	Health state	RR ratio	Lower CI	Upper CI	SE
Moderate OR Severe exacerbation	GOLD 1	[redacted]	[redacted]	[redacted]	[redacted]
	GOLD 2	[redacted]	[redacted]	[redacted]	[redacted]
	GOLD 3	[redacted]	[redacted]	[redacted]	[redacted]
	GOLD 4	[redacted]	[redacted]	[redacted]	[redacted]
Responders	**Health state**	**RR ratio**	**Lower CI**	**Upper CI**	**SE**
Moderate OR severe exacerbation	GOLD 1	[redacted]	[redacted]	[redacted]	[redacted]
	GOLD 2	[redacted]	[redacted]	[redacted]	[redacted]
	GOLD 3	[redacted]	[redacted]	[redacted]	[redacted]
	GOLD 4	[redacted]	[redacted]	[redacted]	[redacted]

The RR ratios for GOLD stage 1 and 4 in the EAG preferred inputs suggest that patients receive considerably worse outcomes when treated with dupilumab. This has no face validity and is likely an artifact of the small patient populations in these health states. More recent GOLD guidelines (including those for 2025) agree that treatment choices should be made on symptoms and exacerbation history and not on GOLD severity stage, recognising implicitly that treatments can be effective regardless of disease FEV1 severity. It is much more likely that dupilumab will have a similar treatment effect regardless of GOLD stage and this can be seen across the rest of the data sets where the RR ratios are more consistent. Under the individualised approach the RR ratios for All Patients and Responder populations is 1.03 and 0.7 respectively. (Table 6). These values are more credible and consistent, further supporting the use of the 'individualised' approach to calculating the means and the bootstrapping methodology to generate SE's.

The updated EAG model results ('Unadjusted' method) are provided below alongside the Sanofi results (Individualised' method) for comparison.

Table 8. Updated model results: Probabilistic

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Sanofi model results from the 'Individualised' analysis							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Background Therapy	[redacted]	[redacted]	[redacted]				
EAG preferred unadjusted analysis							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Background Therapy	[redacted]	[redacted]	[redacted]				

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Table 9. Updated model results: Deterministic

Treatments	TOTAL LYs	TOTAL QALYs	TOTAL costs	Incr. LYs	Incr. QALYs	Incr. costs	ICER
Sanofi model results from the Individualised' analysis							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Background Therapy	[redacted]	[redacted]	[redacted]				
EAG preferred unadjusted analysis							
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Background Therapy	[redacted]	[redacted]	[redacted]				

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

5. Conclusions

The Committee-preferred approach to the calculation of the moderate OR severe RR ratios undervalues dupilumab by diluting the clinically meaningful (and statistically significant) severe exacerbation benefits that define treatment responders.

This is because the means for the combined moderate OR severe exacerbation event rate are dominated by the much larger moderate event rate and the important impact of severe exacerbations becomes incorrectly diminished. This means that when the combined RR ratios are applied to the severe events in the model the observed benefit for dupilumab, particularly and incorrectly in the responder population, is significantly reduced. Severe events are the most important outcome for patients and drive important real-world clinical and economic outcomes therefore they should be expressed separately in the model and not undervalued in this way.

The EAG have raised concerns that we have deviated from the original unadjusted methodology for the calculation of the means and RR ratios. However, this was done with good scientific rational, to address uncertainties arising from small sample sizes. The preference of the EAG to keep the unadjusted approach seems predicated on nothing more than the fact that this was the original method, and that the alternative 'individualised' methodology appears to favour dupilumab. Neither of which are valid reasons to reject it.

After a review of the unadjusted methodology and a detailed investigation of patient-level data in the various cohorts, for the purposes of responding to the committee request for the combined moderate OR severe exacerbation data, we felt this methodology represented too crude an analysis. Clearly, the unadjusted methodology misrepresents the data due to not taking event number and time on treatment for each patient individually into account and also cannot be used to directly derive 95%CIs and SE's for the model. Our updated methodology using individualised means and bootstrapping ensures that the variability in the data is reflected both in the estimates for the RR ratios and their associated SEs, and that the model inputs are as robust as possible given the underlying structure of the data.

We maintain that the most appropriate probabilistic ICER is [redacted] (updated to include all committee preferred assumptions with 14.2 % CFR but maintaining separate implementation of the moderate exacerbation and severe exacerbation RR ratios). However, we have calculated the probabilistic ICER within the constraints of the committees preferred approach using the 'individualised' methodology. This is [redacted] and represents a more credible valuation of

dupilumab than the EAG approach (probabilistic ICER = [redacted]) which gives no fair recognition to the severe exacerbation data for responders and disregards the distribution of events.

Appendix A. Histogram plots for annualised rate of exacerbations

Figure 1 Annualised rate of moderate OR severe exacerbations during the on-treatment period in the Dupilumab group – GOLD stage 1

Figure 2 Annualised rate of moderate OR severe exacerbations during the on-treatment period in the Dupilumab group – GOLD stage 2

Figure 3 Annualised rate of moderate OR severe exacerbations during the on-treatment period in the Dupilumab group – GOLD stage 3

Figure 4 Annualised rate of moderate OR severe exacerbations during the on-treatment period in the Dupilumab group – GOLD stage 4

Figure 5 Annualised rate of moderate OR severe exacerbations during the on-treatment period in the SoC group – GOLD stage 1

Figure 6 Annualised rate of moderate OR severe exacerbations during the on-treatment period in the SoC group – GOLD stage 2

Figure 7 Annualised rate of moderate OR severe exacerbations during the on-treatment period in the SoC group – GOLD stage 3

Figure 8 Annualised rate of moderate OR severe exacerbations during the on-treatment period in the SoC group – GOLD stage 4

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

EAG comment on company's additional response

October 2025

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1 EAG comment

1.1.1 Choice of endpoint for exacerbations

The company's response discusses the discrepancy between their preferred approach and the committee's preference for modelling severe exacerbations. While the company used separate data for moderate and severe exacerbations in their base case, the committee preferred the use of combined moderate or severe exacerbation rates. The company highlighted a number of concerns with the committee's preferred approach, including that:

- the combined exacerbation rates overlook statistically significant trial data, which is directly available from the BOREAS and NOTUS trials;
- the assumption that moderate and severe exacerbations would be reduced by a similar magnitude is not applicable to the responder population; and
- the approach underestimates the clinically meaningful and statistically significant benefits for severe exacerbations that are experienced by the responder population with dupilumab.

As discussed in the original EAG report, the pooled data from BOREAS and NOTUS demonstrated a statistically significant decrease in the combined rate of moderate or severe exacerbations for patients treated with dupilumab. However, this was driven by a reduction in moderate exacerbations, with no statistically significant difference demonstrated for severe exacerbations. While the committee were satisfied that dupilumab was likely to reduce the number of severe exacerbations, the small event numbers and wide 95% CIs meant there was considerable uncertainty regarding the magnitude of this reduction. These concerns led the committee to prefer the use of combined moderate or severe exacerbation rates in the model, rather than the non-significant results for severe exacerbations.

Although the company reported statistically significant reductions in severe exacerbations for the responder cohort, the EAG has previously expressed its concerns about this population. Notably, the ability to demonstrate statistical significance requires a prospective trial which prespecifies the population of interest. The responder cohort was not pre-specified in the BOREAS and NOTUS trials, thereby limiting conclusions on statistical significance for this group. Conclusions are further limited by the need to break randomisation for the analysis, which introduces additional uncertainties. The EAG also notes the small number of severe exacerbation events reported in the dupilumab arm for this group, shown in Table 1. As such, the uncertainties associated with the small number of

exacerbations appear to be further increased by the use of severe, rather than combined moderate or severe, exacerbations.

Table 1. Data on severe exacerbations used to inform the company's favoured approach for relative risk ratios. Data taken from Table 1.38.1 and 1.39.1 of Sanofi - summary of *post-hoc* analyses for Markov cost-effectiveness (CE) model

	Gold Grade 1		Gold Grade 2		Gold Grade 3		Gold Grade 4	
	PBO	Dup	PBO	Dup	PBO	Dup	PBO	Dup
All patients								
Number of participants with >=1 severe exacerbation event (with or without moderate)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of severe exacerbations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responders								
Number of participants with >=1 severe exacerbation event (with or without moderate)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of severe exacerbations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Dup, dupilumab; PBO, placebo

The company's key concern about the use of combined exacerbation rates appears to be the assumption that dupilumab reduces moderate and severe exacerbations equally. While they consider this a valid assumption for the full patient cohort, they do not consider it applicable to responders, noting that, "*Responders in the model are a population which has been selected primarily on achieving a severe exacerbation reduction*". It is unclear to the EAG why the *mechanism* for reduction in severe and moderate exacerbations would differ between the wider patient population and the responder cohort, particularly as the company's clinical experts stated that the mechanism for moderate and severe exacerbations is broadly similar and are driven by the same triggers and biology. Additionally, while it is true that a reduction in severe exacerbations is the main criteria for responders, the EAG notes that the response criteria applied by the company was a combined response, as noted in the company submission, in which, "*a patient is considered a non-responder if they experience more severe exacerbations than the year prior to treatment AND/OR, in case of equal number of severe exacerbation if they experience more moderate exacerbations than the year prior to treatment. All other cases are considered responders*". Given that the criteria to

identify responders is based on a combination of moderate and severe exacerbations, it is unclear why the use of a combined outcome to assess the effects of dupilumab is inappropriate.

While the EAG acknowledges that dupilumab is likely to result in greater reductions in severe exacerbations for the responder cohort than the wider patient group, it does not consider that the company's response addresses the committee's underlying reason for preferring the combined outcome of moderate or severe exacerbations. As discussed above, this decision was based on uncertainties regarding the magnitude of the reduction of severe exacerbations with dupilumab. The use of severe exacerbations for the responder cohort does not appear to reduce this uncertainty, particularly given the smaller patient numbers and fewer severe exacerbations in this group.

The EAG notes that a reduction in severe exacerbations is still included in the economic model for responders, and as such, so are the benefits of a reduction in severe exacerbations (e.g. quality of life, mortality risk, future rate of exacerbations). The difference in the committee preferred assumption and the company's is the magnitude of the reduction in severe exacerbations, which as previously discussed, is considered to be subject to a high degree of uncertainty. The EAG notes that the RRs for responders are applied for the lifetime of the model while patients remain on treatment and therefore considers that applying the combined rates reduces uncertainty, for both the 'responders' and 'all patients' populations.

1.1.2 Methodology used to calculate event rates and relative risk ratios

The EAG thanks the company for providing details on the method used to calculate the relative risk ratios in their latest response. The company stated that, "*The preference of the EAG to keep the unadjusted approach seems predicated on nothing more than the fact that this was the original method, and that the alternative 'individualised' methodology appears to favour dupilumab.*". As previously noted in the EAG response, it was unclear how the individual annualised rates had been calculated, and the company had not provided any justification as to why they had changed their approach. The EAG also noted that, "The combined rate for moderate and severe exacerbations *appears* to be simply adding the individual annualised mean rate for moderate exacerbations and the individual annualised mean rate for severe exacerbations together". As such, in consideration of the information available to the EAG at the time, the EAG deemed the 'unadjusted annualised rate' the most appropriate as it was clear how these had been calculated and was previously the company's preferred appraoch.

Following the company's latest response providing further explanation on how the individual annualised rates have been derived, the EAG agrees that this is the most appropriate method, and as such, agrees with the updated ICER provided in Table 8 of the company's response ([redacted] probabilistic).