For public – redacted

Dupilumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease [ID6235]

Second committee meeting [ACM2]

Technology appraisal committee A [5 August 2025]

Chair: Radha Todd

External assessment group: BMJ Technology Assessment Group

Technical team: Dilan Savani, Anna Willis, Zoe Charles, Janet Robertson and Ian Watson

Company: Sanofi

Dupilumab for treating moderate to severe chronic obstructive pulmonary disease

- ✓ **Recap and key issues**
- ❑ Draft guidance consultation responses summary
- ❑ Company's additional analysis and EAG critique
- ❑ Summary

NICE National Institute for Health and Care Excellence

Key committee questions

Dupilumab (Dupixent®, Sanofi)

Marketing authorisation	• Indicated in "adults as add-on maintenance treatment for uncontrolled COPD characterised by **raised blood eosinophils (EOS**) on a combination of an inhaled corticosteroid (ICS), a long-acting beta2- agonist (LABA), and a long-acting muscarinic antagonist (LAMA), or on a combination of a LABA and a LAMA if ICS is not appropriate" • UK marketing authorisation granted September 2024
Mechanism of action	Recombinant human IgG4 monoclonal antibody that inhibits IL-4 and IL-13 signalling resulting in decrease in mediators of Type 2 inflammation
Administration	• 300mg given every other week as self-administered subcutaneous injection • **Stopping rule** (proposed by company and included in base case model): assess response at 12 months and discontinue if the number of severe exacerbations on treatment is higher than the year prior to treatment. In the case of equal numbers of severe exacerbations, discontinue if the number of moderate exacerbations on treatment is higher than the year prior to treatment
Price	• List price per pack of 2 x 300mg pre-filled pens or pre-filled syringes: £1,264.89 • List price for 12 months of treatment: £16,500 • Agreed patient access scheme

- If dupilumab were to be recommended, how should 'raised eosinophils' be defined in the guidance? Is the company's definition of '300 cells per microlitre or more' used in the trials appropriate?
- Is the proposed stopping rule appropriate for dupilumab?

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COPD, Chronic obstructive pulmonary disease; EOS, Eosinophils; ICS, Inhaled corticosteroids; IgG4, Immunoglobulin G4; IL, Interleukin; LABA, Long-acting beta2- agonist; LAMA, Long-acting muscarinic antagonist

Committee's key conclusions from ACM1

Dupilumab should not be used; further information needed to decide all preferred assumptions

Issue	Committee's preferred assumption
Comparator(s)	• Standard care without dupilumab is appropriate comparator
Model structure	• Suitable for decision making but concerns about some assumptions
Long-term annual decline in FEV_1	• Inform transition probabilities between COPD severity states using Fenwick et al., with multiplier of 1.52 to account for increased rate of decline in people with raised EOS
Rate of severe exacerbations	• Rate ratios used to calculate rate of exacerbations for dupilumab arm highly uncertain • **Further evidence required**
Dupilumab long-term treatment effect	• Assumption that treatment effect maintained throughout lifetime of model highly uncertain • **Further evidence required**
Excess mortality for severe exacerbations	• Highly uncertain whether survival predictions in base cases or scenarios presented reflected clinical practice • Modelling survival benefit for dupilumab highly uncertain • **Further evidence required**
Utility values	• Use values derived from utility regression model including only statistically significant covariates (i.e. non-treatment arm specific utility values)
Acceptable ICER	• Around £20,000 per QALY

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ACM1, Appraisal committee meeting 1; COPD, Chronic obstructive pulmonary disease; EOS, Eosinophils; FEV1, forced expiratory volume in the first second; ICER, Incremental cost effectiveness ratio, QALY, Quality-adjusted life year

Committee's requests for additional analysis

Issue	Request	Provided?
Rate of severe exacerbations	• further evidence to show whether the magnitude of reduction in severe exacerbations in BOREAS and NOTUS was applicable to clinical practice	Yes
Long-term treatment effect	• evidence to support assumption of maintained treatment benefit for dupilumab for lifetime of model	Yes
Excess mortality for severe exacerbations	• data on real-world survival for appraisal population	Yes
	• data estimating mortality attributable to exacerbations	Yes
	• further evidence to support using both a case fatality rate (CFR) to account for the increased risk of mortality from severe exacerbations, and standardised mortality ratios (SMR) to estimate mortality associated with COPD severity	Yes
	• alternative sources of evidence for CFR (if separate CFR supported by evidence)	Yes but states original source of CFR most robust (Hoogendoorn study)
	• scenario applying a CFR from exacerbations, without application of SMRs	Yes but maintains use of CFR and SMR in base case

CFR, Case fatality rate; COPD, Chronic obstructive pulmonary disease; SMR, Standardised mortality ratio

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Consultation responses to draft guidance summary (1)

See appendix for further responses

NICE received several responses from stakeholders and the public expressing concern about the draft guidance:

- Patient and professional organisations:
  - British Thoracic Society
  - Association of Respiratory Nurses
  - Joint response from Taskforce for Lung Health and Asthma + Lung UK
- NHS England
- Company (Sanofi)
- 7 web (public) commentators

Shortly before the committee meeting, NICE also received comments from the clinical expert and 1 further set of web comments – these have been presented to committee as part of the committee papers

Consultation responses to draft guidance summary (2)

See appendix for further responses

High unmet need for new and effective treatments

British Thoracic Society

- Dupilumab first new and effective treatment for 20 years in COPD and potential for many people to benefit
- COPD 3rd largest cause of mortality and 4th largest cause of disability adjusted life years in UK

Association of respiratory nurses

- Negative recommendation will negatively impact people who are likely to benefit from this treatment; impact on patient cannot be restricted to financial impact

Taskforce for Lung Health and Asthma + Lung UK

- Too many people having triple therapy still face significant lung function decline and people with eosinophilic COPD trapped in cycle of exacerbations → dupilumab would provide hope for better future (research shows hope amongst COPD patients leads to improved overall outcomes)
- Every year ~40,000 people die from COPD in UK; 2nd worst death rate for COPD in Europe

Web comments

- Dupilumab would provide much needed treatment option for people with eosinophilic COPD who continue to exacerbate despite maximum treatment

Consultation responses to draft guidance summary (3)

See appendix for further responses

Outcomes

British Thoracic Society

- Any improvement in FEV is a clinical improvement in a condition with non-reversible lung function
- Clinical consensus that <20% reduction of exacerbations 'is plenty'. Preventing 1 exacerbation is likely to prevent multiple exacerbations; potentially even better efficacy in 'super-exacerbators'
- Literature suggests dupilumab would reduce admissions by ~33%; also reduced need for oral corticosteroids

Association of Respiratory Nurses

- People who have acute exacerbations are at an increased risk of future exacerbations and CV events→ potential to reduce risk of CV events if risk of acute exacerbations is decreased

Web comments

- Reported improvements in dupilumab trials clinically meaningful → even small improvements can prevent hospitalisation and reduce corticosteroid use
- Whittaker et al (2024) highlights importance of reducing exacerbations - shows that one third of all who died with COPD died within a month of an exacerbation

COPD, Chronic obstructive pulmonary disease; CV, Cardiovascular; FEV, Forced expiratory volume

Consultation responses to draft guidance summary (4)

See appendix for further responses

Modelling assumptions/parameters

British Thoracic Society

- Questions mortality as an outcome as not primary outcome of trials: disadvantages those disabled with COPD
- Assumptions required to inform severe exacerbations and mortality. Reducing exacerbations will reduce hospitalisations and deaths

Association of respiratory nurses

- Data used to underpin model appears to inaccurately predict clinical benefits of dupilumab for this population and focus on mortality data is misplaced

Web comments

- Concern that EAG model underestimates burden of COPD exacerbations and potential impact of dupilumab
  - critical to recognise the impact of exacerbations on subsequent disease course
- Model appears to assume exacerbation rates remain constant but evidence that exacerbations become more frequent and severe over time→ long term benefit of dupilumab may be underestimated
- Likely underestimation of benefits and cost effectiveness of dupilumab as not all mortality relating to COPD accounted for in data (e.g. increased risk of CV and death following exacerbation)
- Cost savings underestimated as model does not fully capture reduction in severe exacerbations and healthcare utilisation demonstrated in real-world studies
- DECAF score or PEARL score* data relevant to the evaluation rather than sole use of Whittaker et al.

*PEARL score predicts 90-day readmission or death after hospitalisation for acute exacerbation of COPD; DECAF score predicts in-hospital mortality in acute COPD exacerbation

COPD, Chronic obstructive pulmonary disease; CV, Cardiovascular; EAG, External Assessment Group

Consultation responses to draft guidance summary (5)

Health inequalities

See appendix for equality issues raised before consultation

Company (Sanofi):

- Suggests reconsideration of health inequalities issue, with COPD being an identified health inequalities priority for NHS England

British Thoracic society:

- People with COPD often disadvantaged through social inequalities, are typically older and have co-morbidities → disadvantaged compared with other populations. COPD also considered a disability
- Seems to be general opinion that 'they done it to themselves by smoking' but not also considered for heart disease or diabetes/obesity, which are equally linked to lifestyle – morally wrong to deny effective treatment

Taskforce for Lung Health and Asthma + Lung UK:

- Poorest people with COPD have more exacerbations and increased risk of death
- Equality considerations should be central to the appraisal. Committee must consider how new medicines may improve COPD care pathway and increase access to basic care for COPD patients most in need

Web comments

- COPD and exacerbations more prevalent in people of lower socioeconomic backgrounds, and impact of higher admissions during winter felt most acutely in this population
- People with COPD are a disadvantaged group; within NICE's remit to ensure this characteristic is not allowed to further increase health inequalities

COPD, Chronic obstructive pulmonary disease

Consultation responses to draft guidance summary (6)

Acceptable ICER (£20k per QALY in draft guidance)

Company (Sanofi)

- Uncertainties identified by committee addressed in response to draft guidance and increased certainty→ threshold towards the upper end of NICE's WTP threshold more suitable

Association of Respiratory Nurses

- Recommendations imply that the lives of people with COPD are worth less than those of people living with asthma - has an impact with respect to equity of access to treatment when comparing the 2 conditions

British Thoracic Society

- The bar to cross seems higher than other conditions - questions 20k threshold; other conditions, including asthma, have used 30k threshold [tech team note: some previous asthma appraisals used 20K threshold (e.g. TA1045)]

Web comments

- Higher threshold for interventions that reduce exacerbations justified to address current health inequalities

Uncaptured benefits

Uncaptured benefits in company submission

Taskforce for Lung Health and Asthma + Lung UK

- Every year £1.7 billion loss in productivity in England due to COPD-related illness and premature death
- Reducing exacerbations vital to addressing NHS winter pressures → higher incidence of exacerbations in winter
- Around one quarter of people not in work due to COPD→ dupilumab has potential to help many return to work

Web comments

- Important to consider wider environmental and societal impact and carer burden associated with exacerbations

Financial and delivery impact

see appendix for NHS England comments

COPD, Chronic obstructive pulmonary disease; TA, Technology appraisal; WTP, Willingness to pay

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Key issue: Differences in the rate of severe exacerbations between treatment arms (1)

Background

- Dupilumab treatment effect for exacerbations based on rate ratio of annual exacerbations in each treatment arm from pooled trials, with different rate ratios applied for moderate and severe exacerbations
- At ACM1, committee concluded rate ratios used to calculate rate of severe exacerbations for dupilumab arm highly uncertain and further evidence required – see committee's requests

Company

- 32.6% reduction of severe exacerbations with dupilumab vs. placebo in pooled trials, and difference between trial arms (p=0.0725) is close to conventional threshold for statistical significance
- Similar magnitude of reduction also achieved for moderate exacerbations (31.1%; p<0.0001)
- For people who completed 52 weeks of treatment ('on-treatment population'), p value improves to 0.0265→ more appropriate as in real world, people who do not respond to dupilumab would return to SoC alone
- Model includes a responder criterion for continued treatment at week 52 that would likely apply in clinical practice
- For people meeting responder criterion, p value for reduction in severe exacerbation is <0.0001
- Delaying severe exacerbations also clinically meaningful; delay in time to first severe exacerbation statistically significant (p=0.0160) – see appendix for summary of severe exacerbation data from pooled trials
- Small number of severe exacerbations experienced in trials caused by COVID-19 pandemic due to concerns attending hospital; supported by clinical expert opinion and data – see appendix

ACM1, Appraisal committee meeting 1; SoC standard of care

Key issue: Differences in the rate of severe exacerbations between treatment arms (2)

Company

- Tipping point analysis shows reclassifying 6 of 698 moderate events in placebo arm as severe would yield a statistically significant p-value of 0.045
- Reduction in severe exacerbations would have major implications for NHS resource use

Rate ratio for exacerbation by GOLD severity of dupilumab + background therapy vs. background therapy (ITT population)

GOLD severity	Dupilumab + background therapy vs background therapy alone			
	All Patients		Responders	
	Moderate Exacerbation	Severe Exacerbation	Moderate Exacerbation	Severe Exacerbation
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]
Very Severe	[redacted]	[redacted]	[redacted]	[redacted]

EAG comments

- Calculated rate ratios (table above, responder column) in moderate to severe COPD groups for severe exacerbations are much larger than reported reduction in all severe exacerbations noted by company of 0.674 (32.6%) → splitting patients based on COPD severity reduced small numbers in each group with a severe exacerbation even further, increasing uncertainty
- 32.6% (RR 0.674; 95% CI: 0.438 to 1.037) estimate for reduction of severe exacerbations vs. placebo includes wide CIs → could range from a 56.2% reduction to an increase of 3.7% with dupilumab → high uncertainty
- Unclear why tipping-point analysis only considered reclassification of exacerbations in placebo arm
- Tipping point analysis demonstrates results may be sensitive to wrong classification but does not address uncertainty reflected in wide 95% CIs or help to inform precise estimate of reduction in severe exacerbations

*Assumed to be the same as severe due to no exacerbations for very severe patients observed in the dupilumab arm

CI, Confidence interval; COPD, Chronic obstructive pulmonary disease; EAG, External Assessment Group; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ITT, Intention to treat; RR, Rate ratio

Key issue: Differences in the rate of severe exacerbations between treatment arms (3)

EAG comments

- Other analyses reported by company (time to first severe exacerbation and 'on-treatment' analysis) are post-hoc analyses which break randomisation and do not appear to address uncertainties highlighted by committee
- As supported by clinical experts, mechanism for moderate and severe exacerbations is broadly similar and rate reduction would be expected to be similar
- In model, magnitude of reduction for severe exacerbations much larger than that for moderate exacerbations
- For updated base case, prefers to apply rate ratios derived from moderate exacerbations for each COPD severity, to severe exacerbations (preference would have been applying rate ratios for combined moderate and severe exacerbations but data not available to EAG) → notes its approach could be considered optimistic

British Thoracic Society: fewer severe events in trials due to COVID: impact of dupilumab likely to be the same or greater in real life

Web comments: reductions in moderate exacerbations expected to translate into reductions in severe exacerbations → not biologically plausible that moderate exacerbations are reduced but not severe events

Clinical expert: Highlights real-world data on dupilumab from Freud et al. (n=23) which compared outcomes for people with COPD pre- and post- dupilumab treatment – noted a 55% reduction in both moderate and severe exacerbations from baseline (not reviewed by EAG)

To calculate the rate of severe exacerbations for each COPD severity state in the dupilumab arm, does the committee prefer using rate ratios based on moderate or severe exacerbations from dupilumab trials?

COPD, Chronic obstructive pulmonary disease; DG, Draft guidance; EAG, External Assessment Group

Key issue: Excess mortality for severe exacerbations (1)

Key committee questions
Predicted survival in updated models

Background

- In model, excess mortality accounted for via standardised mortality ratio (SMR) associated with each COPD severity stage (from Whittaker et al. 2024), and a separate case fatality rate (CFR) per severe exacerbation
- Committee considered plausibility of modelled survival predictions in both arms and modelled survival benefit of dupilumab relative to background therapy uncertain; requested further evidence – see committee's requests

1. Data on real world survival

Company

- Lack of published real-world survival estimates for specific population of interest but aimed to match the population as closely as possible; provided estimates from 3 key sources (table below) and published literature
- Estimated median survival in these datasets is between 6.9 and 8.7 years → validates updated economic modelling which predicts ~ 8 years for background therapy arm
- Limitations associated with all sources:
  - HES data: time dependent data not available
  - BREATHE data: may overestimate survival as population not type 2 and favourable outcomes in French setting compared with UK
  - MarketScan data: may overestimate survival as population not type 2

Characteristic	Study			
	BOREAS/ NOTUS pooled	England – HES database (2010 to 2019)	France – BREATHE study (2015 to 2021)	USA – MarketScan database (2018 to 2022)
Age, years	65.1	69.97	68.88	Age range used: 65 to 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

* based on company's updated economic model

COPD, Chronic obstructive pulmonary disease; CFR, Case fatality rate; HES, Hospital episode statistics; SMR, standardised mortality ratio

Key issue: Excess mortality for severe exacerbations (2)

Company - Data on real world survival continued

- Most applicable analysis to current appraisal is HES dataset - included a cohort of 3,747 people in England closely matched to inclusion criteria of the BOREAS/NOTUS trial population
- As time-dependent mortality data not available from HES data, median survival calculated assuming exponential decline, giving estimated median survival of 6.9 years
- See appendix for supplementary evidence to support impact of COPD on mortality risk

EAG comments

- Exponential model to calculate median survival from HES database unlikely to be fully representative of mortality over time for a progressive condition such as COPD
- Comparisons of median survival from RWD with modelled outputs based on BORUS/NOTUS trials uncertain due to differences in key characteristics between populations such as age, sex and proportion of current smokers (see RWD table)→ caution needed in interpreting results
- Notes that company's additional analyses do not invalidate company's model estimates
- Provides scenario with model start age of 69 (instead of age 65 based on trial data) based on RWE provided by company → reduces median survival in EAG base case to be similar to that of company base case for background therapy only arm

Key issue: Excess mortality for severe exacerbations (3)

2. Mortality attributable to exacerbations

Company

- Based on HES dataset population, of 1,522 deaths during follow up, 601 related to exacerbations (39.5%)→ aligns with base case in which 41% of mortality related to exacerbations and 53% due to COPD severity stage
- Notes estimates do not add to 100% as based on mortality in Markov section of model (not possible to attribute source of deaths in one-year decision tree section of model)

EAG comments

- Notes that, of the 94% of deaths in Markov model, 43.6% were due to severe exacerbations→ reassuring that proportion of deaths from exacerbations in model is largely in line with the HES dataset (39.5%)
- Some caution may be needed when comparing model outputs to RWD analysis due to differences in key characteristics between populations

COPD, Chronic obstructive pulmonary disease; EAG, External Assessment Group; HES, Hospital episode statistics; RWD, Real world data

Key issue: Excess mortality for severe exacerbations (4)

3. Application of both case fatality rate (CFR) and standardised mortality ratio (SMR)

Company

- Across 4 recent economic models in COPD, all have independently applied a CFR and SMRs – see appendix
- Moderate exacerbations also carry significant risk of mortality → conservative approach only applying CFR for severe exacerbations
- In response to potential of double-counting impact of severe exacerbations using Whittaker et al. 2024 to inform the SMRs and a separate CFR:
  - Whittaker at al. study population less severe than population of interest→ capturing mortality specifically due to severe exacerbations through SMR expected to be very low
  - In Whittaker et al., only 4.3% (14,603 out of 339,647 total patients) had 1 or more severe exacerbations in year prior to baseline (contrast to 26.2% from HES study) → minimal risk of double counting

EAG comments

- On consideration of previous economic models in COPD and impact of severe exacerbations on mortality, EAG considers use of both CFR and SMR to be justified
- Recognises that COPD population in Whittaker study is less severe than population in current appraisal→ applying only these SMRs, with no separate consideration of exacerbations, may overestimate survival
- Based on small (4.3%) proportion of people in Whittaker study who had 1 or more severe exacerbations in year prior to baseline, considers that risk of double counting should be very small

CFR, Case fatality rate; COPD, Chronic obstructive pulmonary disease; EAG, External Assessment Group; HES, Hospital episode statistics; SMR, Standardised mortality ratio

Key issue: Excess mortality for severe exacerbations (5)

4. Alternative sources of evidence for CFR

Company

- Range of alternatives provided for CFR (see appendix) but with exception of Wildman et al. 2009 and Echevaria et al. studies, all increase modelled median survival
- Hoogendoorn et al. 2011 provides most robust estimate for CFR (15.6%) → does not rely on arbitrary timeframes like 30- or 90-day cutoffs and isolates excess mortality directly attributable to the exacerbation
- Mortality impact of severe exacerbation much longer than 90 days → 180-day mortality of 37% in Wildman et al.
- Similar CFR of 15.3% accepted in TA461 from Connolly et al. for roflumilast
- Hoogendoorn et al. based on older (before 2005) non-UK data but treatment practices have changed little and UK mortality remains higher than most of Europe → may even underestimate UK risk
- Provided scenarios exploring the impact on ICER of different rates of CFR on top of the SMR and also scenarios applying a CFR due to exacerbations without application of SMRs – see appendix

EAG comments

- Remains concerned with applicability of studies included in Hoogendoorn et al. as 2005 was most recent data used with all others based on data from 1999 and prior
- Turkey and Denmark have similar rate of mortality to UK and were included in the 6 studies informing Hoogendoorn et al.→ disagrees that CFR in Hoogendoorn et al. may be an underestimate
- EAG in TA461 raised concerns with 15.3% CFR and preferred National Asthma and COPD Audit Programme (NACAP) 2014 data – see appendix

CFR, Case fatality rate; EAG, External Assessment Group; ICER, Incremental cost effectiveness ratio; RWD, Real world data; SMR, Standardised mortality ratio; TA, Technology appraisal

Key issue: Excess mortality for severe exacerbations (6)

EAG comments continued - Alternative sources of evidence for CFR

- Prefers NACAP 2018 to 2020 data for base case as most recent and largest dataset available to provide estimate for CFR of England and Wales (90-day mortality based on 9999 deaths out of 83,994 admissions)
- While using 90-day mortality rate from NACAP data may risk not capturing longer-term increased risk of mortality from severe exacerbations in that year, people are at a higher risk of a severe exacerbation in following model cycle and having CFR applied again
- High uncertainty around true value; Echevaria et al. studies indicate CFR could be higher (17.5%)

Other comments - web comments in response to DG consultation

- In Whittaker et al. 2024, proportion of GOLD D (severe) patients was small → model likely underestimates mortality and cost effectiveness ratio could be artificially inflated
- PEARL score developed in cohort of people with COPD who survived an exacerbation needing hospitalisation across 6 UK hospitals: mortality was 9.7% at 90 days and 23.2% at 1 year excluding inpatient deaths → supports expected median mortality of 4 to 7 years (median survival of ~13 years unrealistic)
- Exacerbations contribute to disease progression and increase risk of CV events which are also associated with significant mortality risk (at least an 8-fold increase in MIs within 7 days of severe exacerbation)

Does committee consider it appropriate to apply a separate mortality impact for severe exacerbations? If so, does committee prefer the CFR estimate from Hoogendoorn et al. 2011 or NACAP 2018 to 2020?

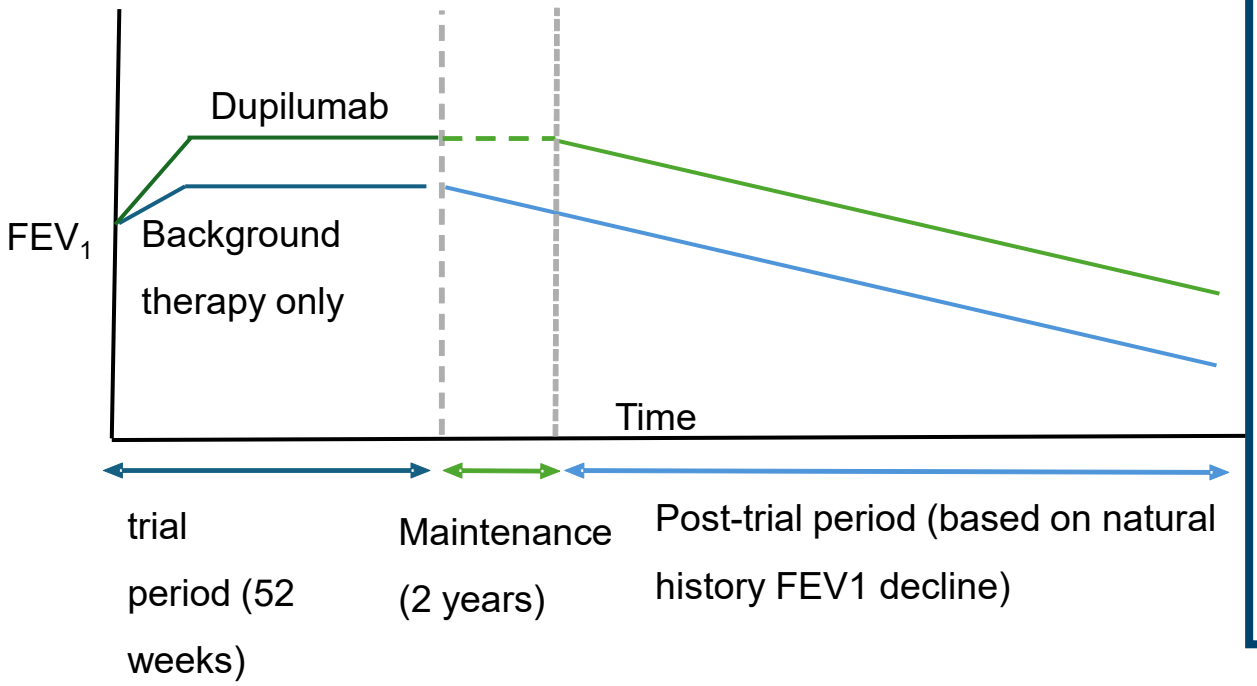
CFR, Case fatality rate; NACAP, National Asthma and COPD Audit Programme; COPD, Chronic obstructive pulmonary disease; CV, Cardiovascular; EAG, External Assessment Group; GOLD, Global Initiative for Chronic Obstructive Lung Disease; MI, Myocardial infarction

Key issue: Long-term treatment effect of dupilumab (1)

Background

- Company's base case assumes a treatment effect maintenance period for dupilumab of 3 years, during which annual FEV_1 does not decline
- Due to higher FEV_1 for people in dupilumab arm at 3 years, a treatment benefit is maintained throughout model lifetime (while people remain on dupilumab) → committee requested further evidence to support assumption

Representation of treatment effect for FEV_1 applied in model



Company

- Long-term asthma data from TRAVERSE show no evidence of waning over 3 years
- Mechanisms of lung function decline broadly similar for Type 2 subsets of both COPD and asthma
- Dupilumab targets IL-4 and IL-3 signalling so addresses core driver of lung function decline
- Conducted further reweighted analysis of subgroup in TRAVERSE study matched to people in pooled dupilumab trials
- Matched based on age, pre-BD FEV_1 and comorbidities to support applicability of asthma population to COPD (4 sets of analyses)

COPD, Chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in the first second; Pre-BD, Pre-bronchodilator

Key issue: Long-term treatment effect of dupilumab (2)

Company

- Updated reweighted analyses results show FEV_1 is maintained in matched populations → selected comorbidities had no impact on ability of dupilumab to maintain FEV_1 treatment effect up to 3 years – see appendix
- Studies in other dupilumab indications do not show treatment effect waning (up to 5 years for atopic dermatitis)
- Data on smoking cessation in COPD demonstrates that FEV_1 improves after stopping smoking, then declines more slowly than in current smokers; similarly not expected that relative FEV_1 benefit vs background therapy would decline and relative benefit may even increase over time – see appendix

EAG comments

- As comorbidities presented in separate analyses, unlikely that all prognostic factors and treatment effect modifiers adjusted for; also unclear why age, pre-BD FEV_1 and comorbidities were only factors chosen for matching
- While most baseline characteristics of the adjusted TRAVERSE population were similar to BOREAS/NOTUS, there were still differences in trial populations (66.8% in BOREAS/NOTUS were male vs 32.2% to 34.5% for TRAVERSE)
- Reassuring that adjusted data sets indicate a sustained benefit of dupilumab but uncertainty remains about potential underlying differences between populations and applicability of TRAVERSE to people with COPD
- Further to FEV_1, treatment effect on rate of exacerbations also remains for lifetime on model while on dupilumab
- Long term treatment effect uncertain but assumes continued treatment benefit for lifetime of model in base case

British Thoracic society: benefit lasts for as long as administered, akin to any other biologic→ MATINEE study (mepolizumab COPD trial) followed people up for 104 weeks and showed benefit in exacerbations until end of trial
Association of respiratory nurses: assumption that benefits may not last do not align with data

Does the committee accept the approach used to model the long term treatment effect for dupilumab in the company and EAG base cases?

COPD, Chronic obstructive pulmonary disease; FEV1, forced expiratory volume in the first second; Pre-BD, Pre-bronchodilator

Summary of company and EAG base case assumptions post ACM1

Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Long term decline in FEV_1 used to inform transition probabilities	Multiplier applied to Fenwick et al. FEV_1 decline	Multiplier applied to Fenwick et al. FEV_1 decline
Rate of severe exacerbations in dupilumab arm	Treatment effect based on rate ratio of annual **severe** exacerbations from dupilumab trials	Treatment effect based on rate ratio of annual **moderate** exacerbations from dupilumab trials due to no significant difference in severe exacerbations
Dupilumab treatment effect maintenance	Assumed treatment effect maintained for 3 years; lifetime benefit vs background therapy maintained for lifetime of model	Assumed treatment effect maintained for 3 years; lifetime benefit vs background therapy maintained for lifetime of model
Case fatality rate (CFR) for severe exacerbations	Hoogendoorn et al (2011): 15.6%	National Asthma and COPD Audit Programme (NACAP): 11.9%
Utility values	Utility values independent of treatment arm	Utility values independent of treatment arm

NICE

EAG, External Assessment Group; FEV_1, forced expiratory volume in the first second; NACAP, National Asthma and COPD Audit Programme

See appendix for scenario analysis

Company base case results – post ACM1

Deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Background Therapy	[redacted]	[redacted]	-	-	-
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Probabilistic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Background Therapy	[redacted]	[redacted]	-	-	-
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NICE ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year

See appendix for scenario analysis

EAG base case results – post ACM1

Deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Background Therapy	[redacted]	[redacted]	-	-	-
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Probabilistic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Background Therapy	[redacted]	[redacted]	-	-	-
Dupilumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NICE ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year

See appendix for scenario analysis

EAG preferred assumptions applied to company base case

EAG's preferred model assumptions, Individual impact (deterministic)

Preferred assumption	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company base case post ACM1	[redacted]	[redacted]	[redacted]
Severe exacerbation RRs equivalent to moderate exacerbation RRs by COPD severity	[redacted]	[redacted]	[redacted]
CFR of 11.9% from NACAP 2018-2022	[redacted]	[redacted]	[redacted]
EAG base case post ACM1	[redacted]	[redacted]	[redacted]

COPD, Chronic obstructive pulmonary disease; RR, rate ratio; CV, cardiovascular; EAG, External Assessment Group; CFR, case fatality rate; NACAP, National Asthma and COPD Audit Programme; ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year; ACM1, appraisal committee meeting 1

Dupilumab for treating moderate to severe chronic obstructive pulmonary disease

- ❑ Recap and key issues
- ❑ Draft guidance consultation responses summary
- ❑ Company's additional analysis and EAG critique
- ✓ **Summary**

NICE National Institute for Health and Care Excellence

Key committee questions

Parameter	Key Committee Questions
Stopping rule	Is the proposed stopping rule appropriate for dupilumab?
Definition of raised EOS	If dupilumab were to be recommended, how should 'raised eosinophils' be defined in the guidance? Is the company's definition of '300 cells per microlitre or more' appropriate (as per BOREAS and NOTUS inclusion criteria) ?
Rate of severe exacerbations	What is the committee's preferred assumption for the rate of severe exacerbations for dupilumab (treatment effect based on the rate ratio of annual severe exacerbations from dupilumab trials or rate ratio of annual moderate exacerbations)?
Long-term treatment effect maintenance	Does the committee accept the approach used to model the long-term treatment effect for dupilumab in the company and EAG base cases?
Excess mortality for severe exacerbations	• Does the committee consider it appropriate to apply a separate mortality impact for severe exacerbations? • If so, what is the committee's preferred approach to model this (CFR estimate from Hoogendoorn et al. 2011 or NACAP 2018 to 2020 data)?
Uncaptured benefits	Are there any uncaptured benefits to be taken into account in decision making?
Equality and health inequality issues	Are there any equality or health inequality issues to be taken into account in decision making?
Preferred ICER and threshold	• What is the committee's preferred ICER threshold – and why? • What is the committee's preferred ICER?

Dupilumab for treating moderate to severe chronic obstructive pulmonary disease

Supplementary appendix

NICE National Institute for Health and Care Excellence

Consultation responses to draft guidance summary (7)

DG consultation responses

Modelling assumptions/parameters

British Thoracic society:

- 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 (more than 120,000 admissions per year in England; PCRS data)

Web comments

- In ETHOS trial, triple therapy reduced exacerbations and mortality, with the greatest reduction seen in people with higher blood eosinophil counts; mortality difference largely due to fewer CV events

Outcomes

Web comments

- A systematic review (MDPI, 2024) and real-world data (Frontiers in Medicine, 2024) demonstrate that dupilumab offers significant benefits across a broader range of people than those included in BOREAS and NOTUS trials, including those with lower eosinophil counts→ current recommendations overly restrictive

COPD, chronic obstructive pulmonary disease; PCRS, Primary Care Respiratory Society; CV, cardiovascular

Consultation responses to draft guidance summary (8)

DG consultation responses

NHS impact

Asthma + Lung UK

- COPD exacerbations account for 1 in 8 UK hospital admissions→ dupilumab would reduce burden from severe exacerbations on NHS
- By 2030, prevalence is projected to rise by 40% and cost of exacerbations is predicted to be £2.5 billion

Web comments

- COPD 2nd most common reason for emergency hospital admission in UK
- Clinical benefits of dupilumab aligned with NHS priorities and government policy due to environmental benefits of lower healthcare resource utilisation driven by reduced exacerbations

Financial and delivery impact of introduction of dupilumab

NHSE

- Generated cost models for different pathway scenarios to be able to compare different requirements needed for real-world scenarios compared to trial conditions
- Results: Incremental per patient costs for initiation & management (year 1) of people having 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

Potential uncaptured benefits

Benefits not captured in QALY calculation, as per company submission:

- **NHS winter pressures**:
  - People with COPD can be significantly affected by cold weather with more symptoms. Dupilumab has potential to relieve NHS pressure by reducing symptoms and admissions for exacerbations
- **Holistic impact of dupilumab on symptoms**
  - Dupilumab associated with greater reduction in E-RS: COPD instrument (patient-reported outcome) vs background therapy. No mapping algorithm to convert to EQ-5D→ benefit may not be fully captured
- **Environmental impact**
  - Implementation of dupilumab for COPD may be carbon neutral or carbon saving through reductions in healthcare resource use because of improved outcomes→ in particular, reduced hospitalisations

COPD, Chronic obstructive pulmonary disease; E-RS, Evaluating Respiratory Symptoms in COPD; QALY, Quality-adjusted life year

Equality considerations summary

Raised by Company, clinical experts and Asthma + Lung UK

- COPD disproportionately affects people of certain demographics
  - Deprived areas have increased prevalence of smoking
  - People from lower socioeconomic backgrounds more likely to develop COPD
  - Age-standardised mortality rates due to COPD highest in the most deprived areas, and in men (especially men of Bangladeshi background)
- Wide regional variation in outcomes:
  - 4-fold difference in mortality rate from COPD depending on geographic region
- Disparities in quality of care:
  - Differential prescribing of pharmacological treatments and rate of referral for COPD rehabilitation between people of different races/ethnicities, and depending on geographical location
  - Higher rate of COPD exacerbations in people from lower socioeconomic backgrounds
  - People from deprived areas find accessing healthcare difficult due to practicality and cost
- Dupilumab can help to reduce health inequalities
  - Can be provided in a “care at home” setting reducing cost of travel and obtaining healthcare for more deprived populations
  - Enable better access to care and not discriminate against those from more deprived areas who tend to smoke more

Back to dupilumab

Key clinical trials

Key evidence for dupilumab came from 2 randomised-controlled trials, BOREAS and NOTUS

	BOREAS	NOTUS
Design	Phase 3, placebo-controlled, double-blind, randomised multicentre, international trial	
Population	People aged 40 to 80 with moderate-to-severe uncontrolled COPD* with evidence of Type 2 inflammation (blood EOS ≥300 cells/μL)	As per BOREAS but with people aged 40 to 85 years
Intervention	Dupilumab subcutaneous 300 mg every 2 weeks + background therapy	
Comparator(s)	Placebo every 2 weeks + background therapy	
Duration	52-week study treatment period + 12-week post-treatment period NOTUS modified to include interim analysis (21.3% did not reach 52-week assessment point)	
Primary outcome	Annualised rate of moderate or severe COPD exacerbations over 52-week treatment period	
Key secondary outcomes	Change from baseline to week 12 and week 52 in FEV1; Change from baseline to week 52 in SGRQ total score and proportion with improvement of ≥4 points in SGRQ score	
Locations	275 sites in 24 countries	329 sites in 29 countries
Used in model?	Yes: FEV_1, exacerbation rate, SGRQ	

* ≥2 moderate or ≥1 severe historical exacerbations within 12 months on LABA + LAMA + ICS (or LABA + LAMA if ICS is not appropriate)

COPD, Chronic obstructive pulmonary disease; EOS, Eosinophil; FEV_1, forced expiratory volume in the first second; ICS, Inhaled corticosteroids; LABA, Long-acting beta2- agonist; LAMA, Long-acting muscarinic antagonist; SGRQ, Saint George's Respiratory Questionnaire

Pooled results, BOREAS and NOTUS: moderate or severe exacerbations

Dupilumab resulted in a statistically significantly reduction in annualised rate of moderate or severe exacerbations compared with placebo over 52 weeks

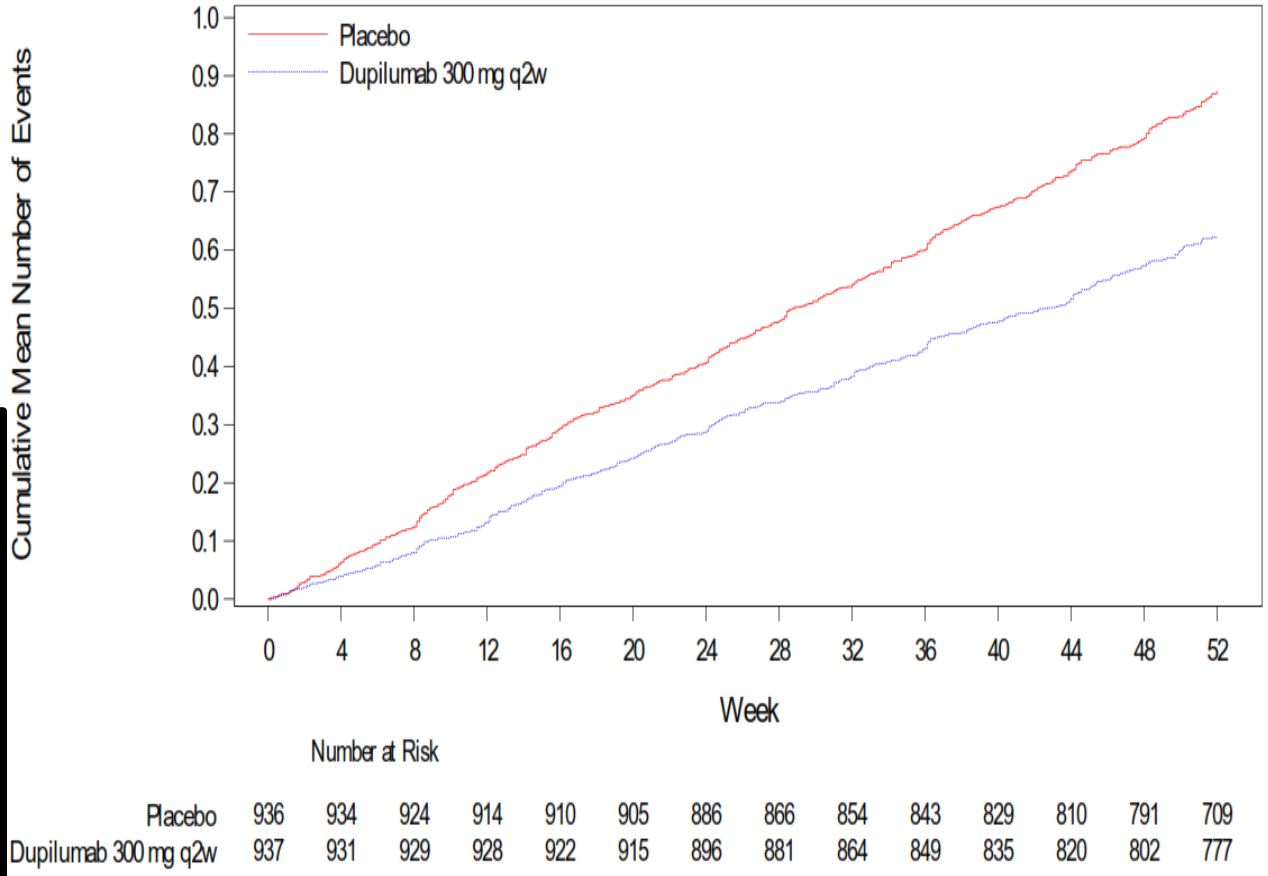
Primary endpoint: Annualised rate of moderate or severe exacerbations of COPD over the 52-week treatment period; pooled results

	Dupilumab (95% CI)	Placebo (95% CI)
Adjusted annualised rate	0.79 (0.69, 0.92)	1.16 (1.01, 1.33)
Rate ratio (95% CI)	0.69 (0.60, 0.79)	

EAG: despite interim analysis used for NOTUS (21.3% did not reach 52-week assessment point), similar results reported as for BOREAS trial →pooled analysis is an accurate reflection of rate of exacerbations over 52-week treatment period

Results meet company's threshold to indicate clinically meaningful difference between treatments. Effects may be modest reflecting difference of 0.37 exacerbations per patient per year or ~ 1 fewer every 3 years

Pooled analysis of the cumulative mean number of moderate or severe COPD exacerbations



NICE COPD, Chronic obstructive pulmonary disease; CI, Confidence interval; Q2W, Every 2 weeks

Pooled results, BOREAS and NOTUS: pre-bronchodilator FEV_1

Dupilumab resulted in statistically significantly improvements in pre-BD FEV_1 compared with placebo at both week 12 and week 52

Key secondary endpoint: week 12 change in pre-BD FEV_1; pooled results

	Dupilumab	Placebo
Week 12 least square mean change from baseline	147ml	64ml
Least square mean difference (95% CI)	83ml (53, 112)	

Key secondary endpoint: week 52 change in pre-BD FEV_1; pooled results

	Dupilumab	Placebo
Week 52 least square mean change from baseline	133ml	59ml
Least square mean difference (95% CI)	73ml (40, 107)	

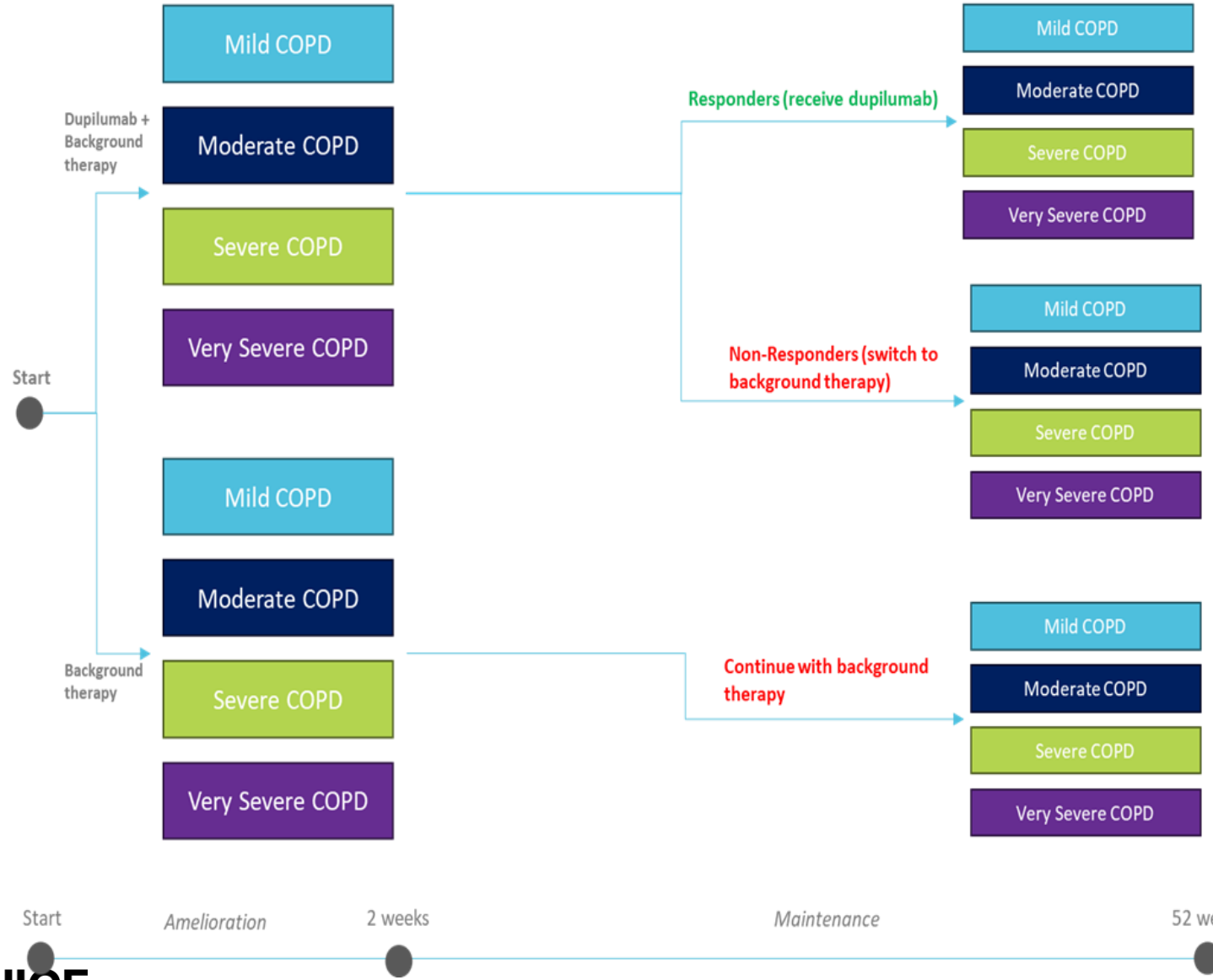
Change in pre-BD FEV_1 smaller in NOTUS than BOREAS. But both reported significantly greater improvements with dupilumab than placebo at 12 and 52 weeks

EAG: results support use of pooled analysis despite interim analysis used for NOTUS. Results meet part of company's threshold to indicate clinically meaningful difference between treatments

NICE CI, Confidence interval; FEV_1, forced expiratory volume in the first second; Pre-BD, Pre-bronchodilator

Company's model (1)

Company produced a short-term decision-tree (52 weeks) leading to a Markov model



People are assigned to 1 of 4 health states at the end of the decision tree (based on severity of COPD):

- 1.GOLD stage 1: mild COPD, ppFEV$_1$ ≥80,
- 2. GOLD stage 2: moderate COPD, ppFEV$_1$ ≥50 and <80,
- 3. GOLD stage 3: severe COPD, ppFEV1 ≥30 and <50,
- 4. GOLD stage 4: very severe COPD, ppFEV1 <30.

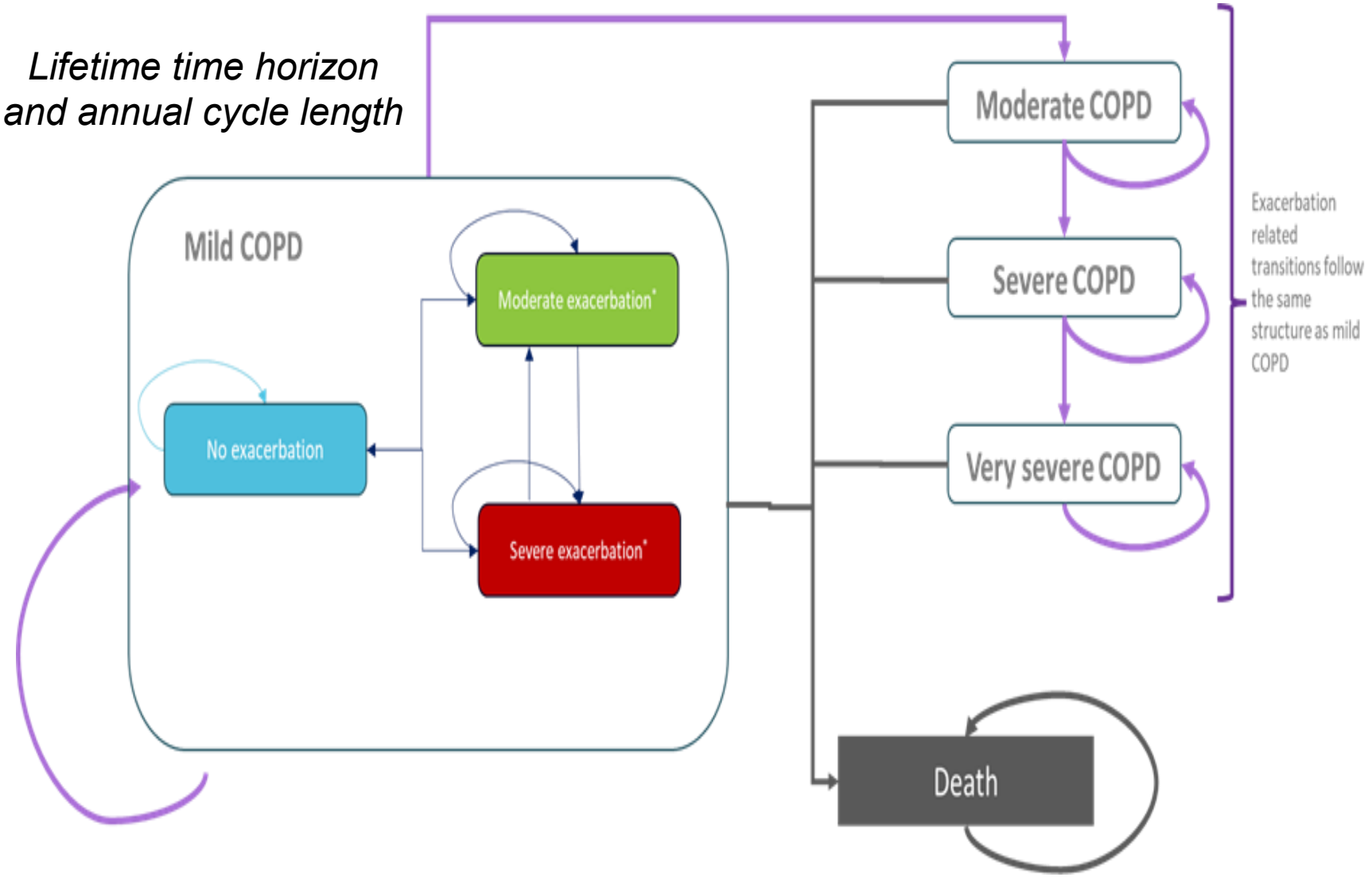
Within COPD severity health states, people are further split based on exacerbation status (no exacerbation, moderate exacerbation and severe exacerbation) and number of exacerbations (1, 2 or ≥3)

COPD, Chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ppFEV$_1$, percentage predicted forced expiratory volume in the first second

Company's model (2)

Company produced a short-term decision-tree (52 weeks) leading to a Markov model

Lifetime time horizon and annual cycle length



- Markov model health states split by both COPD severity and recent exacerbation status (none, ≥1 moderate, ≥1 severe).
- 12 health states plus absorbing death state
- As per decision-tree, exacerbation states further split by number of exacerbations.

EAG: satisfied that model structure captures main features of COPD but limitations with annual cycle length

Key issue main deck

Key issue: Differences in the rate of severe exacerbations between treatment arms

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

mITT, modified Intention-to-treat; SoC, standard of care

Key issue main deck

Key issue: Differences in the rate of severe exacerbations between treatment arms

Company

- Moderate: severe ratio in BOREAS and NOTUS was 11:1→ lower reporting of severe exacerbations due to COVID-19
- Depending on population being studied, generally moderate:severe event ratios are expected to be approximately 4:1 (Mittmann, 2008),
- In recent studies of populations similar to that of BOREAS and NOTUS, ratios of 2:1 to 5:1 have been described (Pavord, 2021; Criner 2019).

Key issue main deck

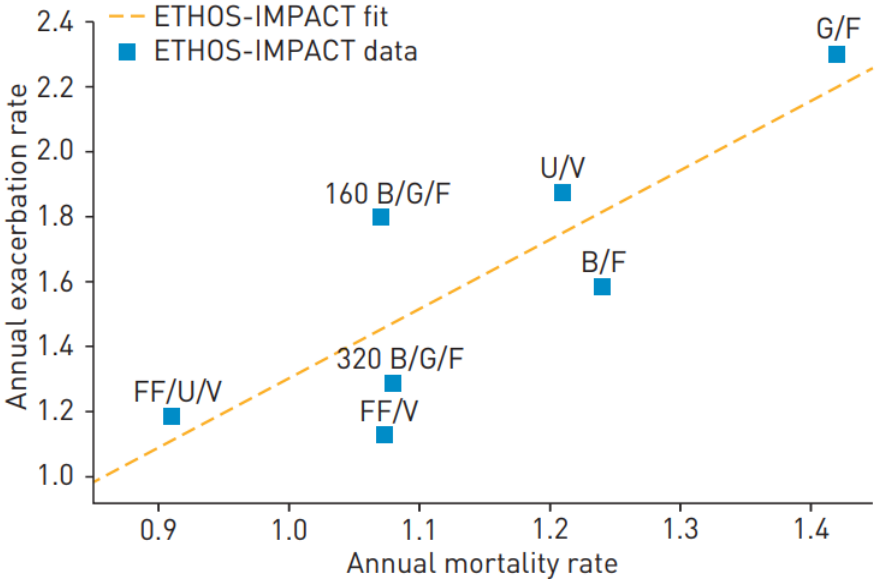
Key issue: Excess mortality for severe exacerbations

Company

Data on real world survival

- Acknowledge not directly applicable to population of interest but recent real-world study (Sun 2024) in US COPD patients having dupilumab for other indications (where COPD was a comorbid disease) found that all-cause mortality reduced by 47% vs. matched patients not having dupilumab (0.53 [95% CI = 0.43-0.65], p < 0.001)
- People with COPD carry substantial increased risk of dying compared with age-matched general population due to progressive decrements to lung function, development of comorbidities (e.g. increased risk of CV events following exacerbation; Løkke 2023) and compounding risk of future exacerbations
- IMPACT and ETHOS (studies of ICS-containing therapies) indicate potentially linear and direct relationship between exacerbation and mortality rates
- Such data supportive of expert clinical opinion that any treatment reducing exacerbations would be expected to reduce mortality

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



CV, cardiovascular; COPD, Chronic obstructive pulmonary disease; ICS, Inhaled corticosteroids

Key issue main deck

Key issue: Excess mortality for severe exacerbations

Company

Application of both case fatality rate (CFR) and standardised mortality ratio (SMR)

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% Hoogendoorn 2011
Leerink Center for Pharmacoeconomics 2025	United states	Dupilumab vs SoC (triple therapy)	(Atsuo 2011)	15.6% Hoogendoorn 2011

CFR, Case fatality rate; EAG, External Assessment Group; SMR, standardised mortality ratio; COPD, Chronic obstructive pulmonary disease

Key issue main deck
Scenario analysis

Key issue: Excess mortality for severe exacerbations

Alternative sources for CFR provided by company	Parameter estimate	SOC Median modelled survival duration (years)
NACAP (30 day mortality)	6.1%	10.4
NACAP (90 day mortality)	11.9%	9.0
Whittaker 2022	Applied as incident rate ratio relative to no exacerbations: 1 Moderate exacerbation 1.08 (1.04 – 1.12) 2 Moderate exacerbations 1.16 (1.10 – 1.22) 3+Moderate exacerbations 1.32 (1.26 – 1.39) 1 Severe exacerbation 1.75 (1.66 – 1.85) 2 Severe exacerbations 2.33 (2.10 – 2.58) 3+Severe exacerbations 2.87 (2.53 – 3.25)	10.4
Roflumilast,TA461 (Connolly 2006)	15.3%	8.3
Wildman 2009	37.9%	5.5
Echevaria 2017 and Echevaria 2022 (90 day mortality)	17.5%	7.96
Echevaria 2022 (1-year mortality)	29.8%	7.17 (applied without SMR to avoid double counting)

- Echevaria data based cohort of 2645 COPD patients with severe exacerbation at 6 English hospitals 2008 to 2014
- Lower 90-day mortality than NACAP; Company states that Echevaria author noted national audit data will often not be physician and spirometry confirmed COPD, so will underestimate impact of COPD exacerbations
- Company states that Echevaria data is based on a more robust diagnosis of severe exacerbation in COPD, more aligned to criteria used in BOREAS & NOTUS studies

NICE

CFR, Case fatality rate; NACAP, National COPD Audit Programme; SoC, Standard of care; COPD, Chronic obstructive pulmonary disease

Key issue main deck

Key issue: Excess mortality for severe exacerbations

EAG comments

Alternative sources of evidence for CFR

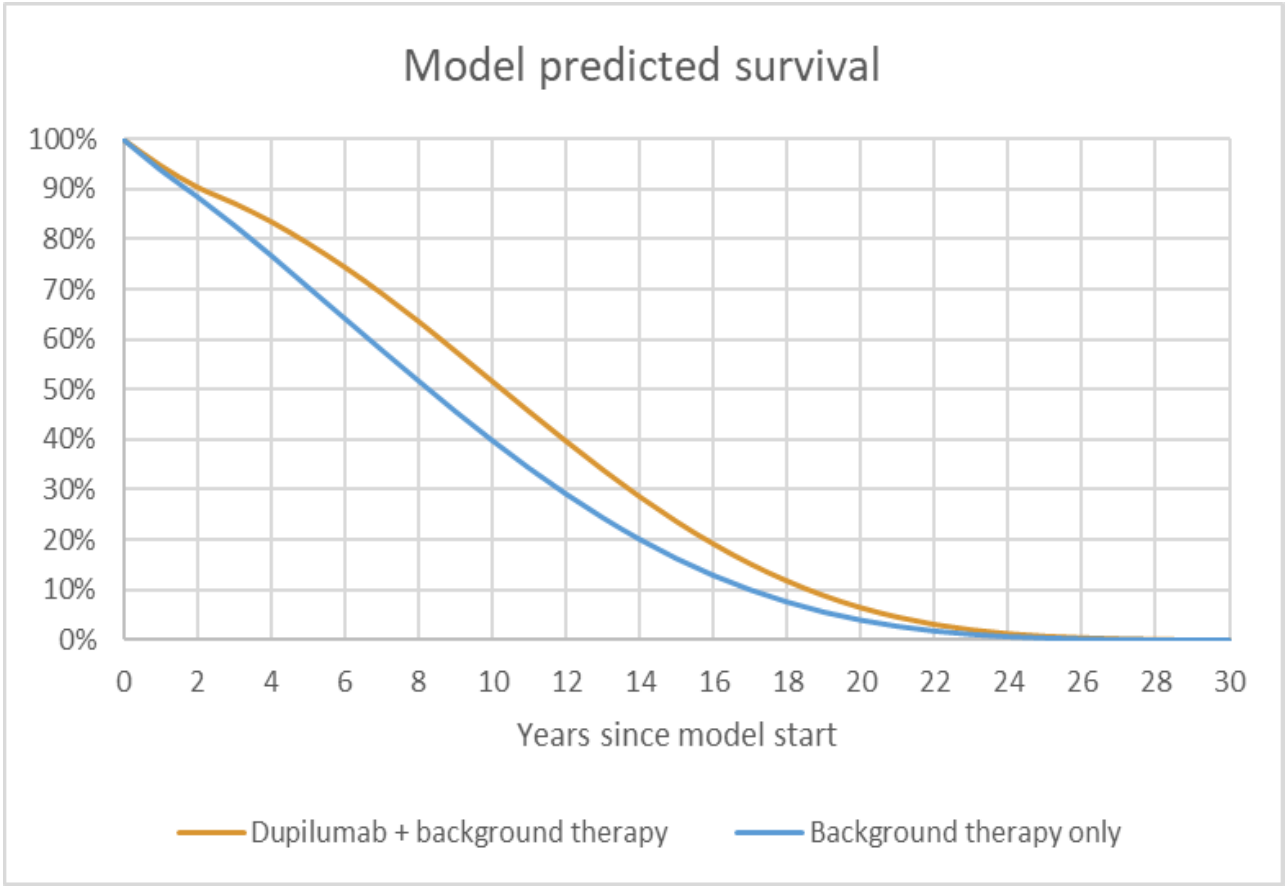
- Company reference Wildman et al. 2009 to support that the mortality impact of a severe exacerbation can be much longer than 90 days but this study is based on people admitted to an intensive care unit or a respiratory high dependency unit → likely to reflect the most severe patients
- Whittaker et al. 2022 incidence rate ratios (IRR) applied to SMRs may be plausible option as this allows risk of moderate and severe exacerbations to be included as is a consistent source of data used but acknowledges company's concerns that this approach may not be fully reflective of patient population
- EAG in TA461 noted that they did not consider 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)

CFR, Case fatality rate; EAG, External Assessment Group; ICER, Incremental cost-effectiveness ratio; SMR, standardised mortality ratio

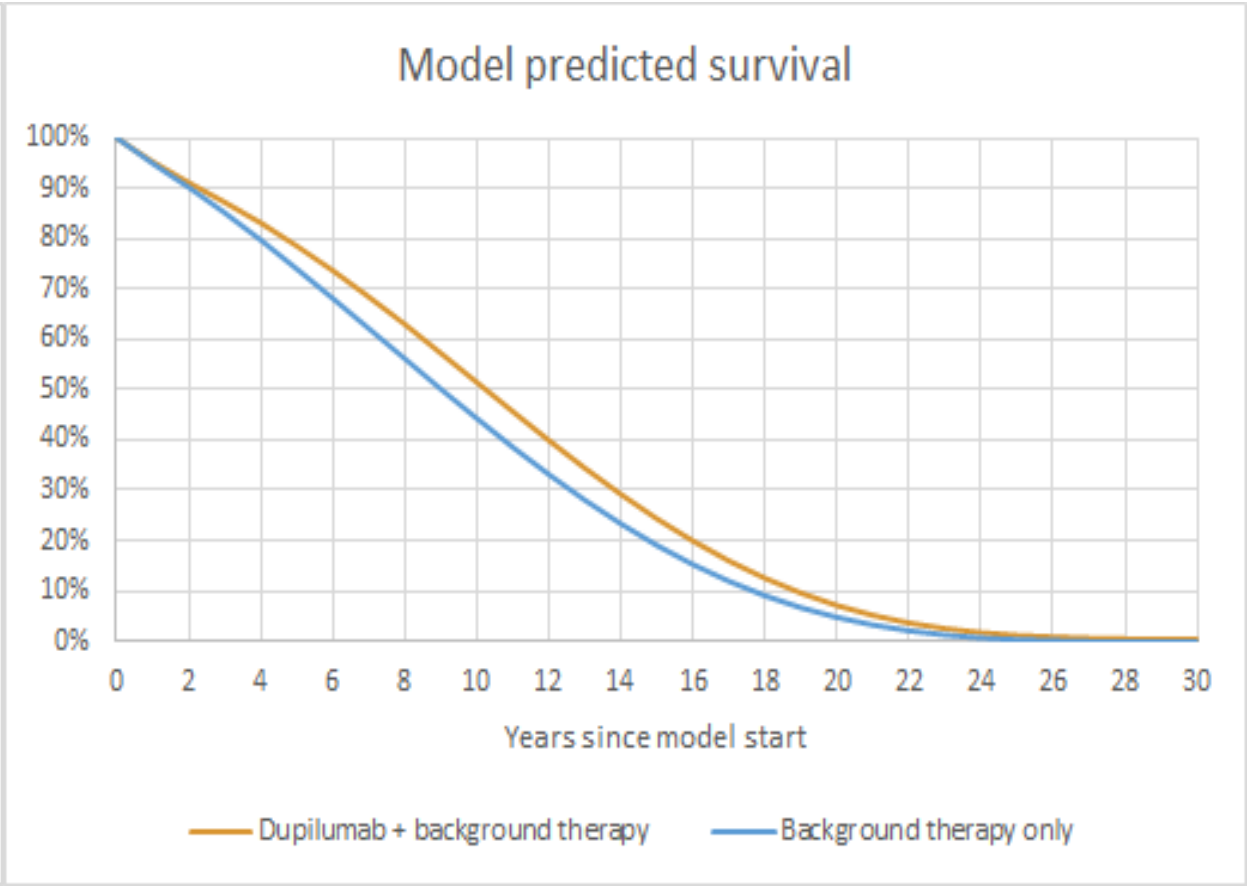
Key issue main deck

Key issue: Excess mortality for severe exacerbations

Model predicted survival in company updated base-case analysis



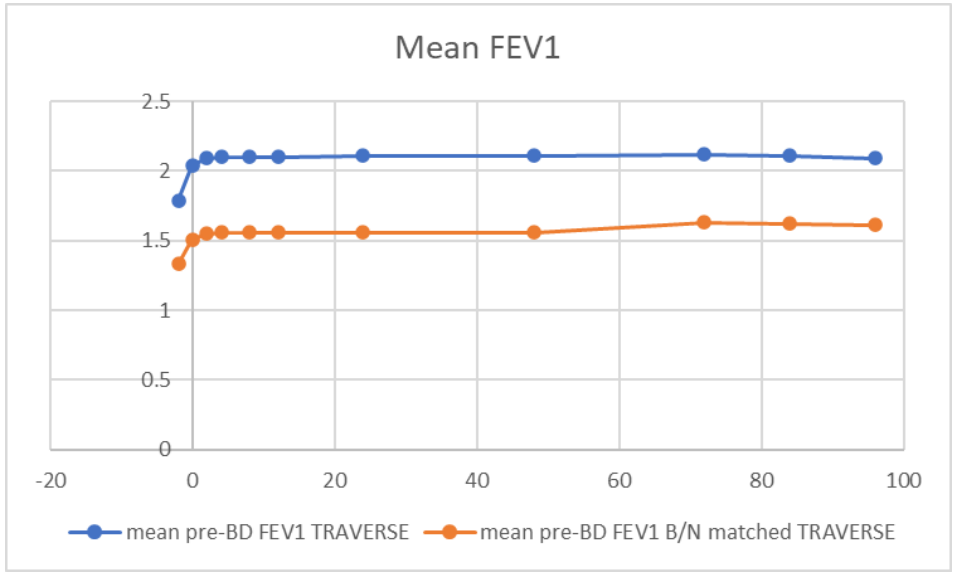
Model predicted survival in EAG updated base-case analysis

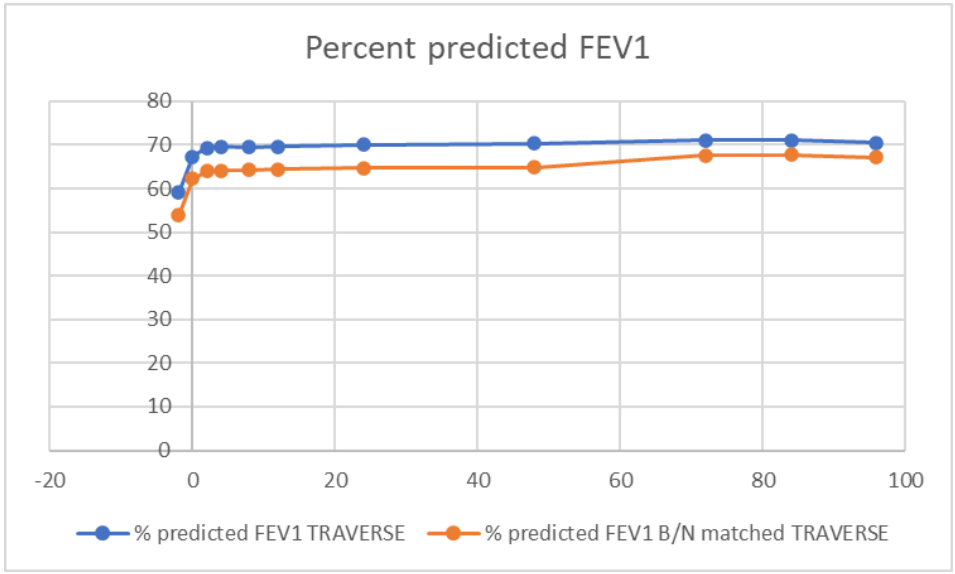


Key issue main deck

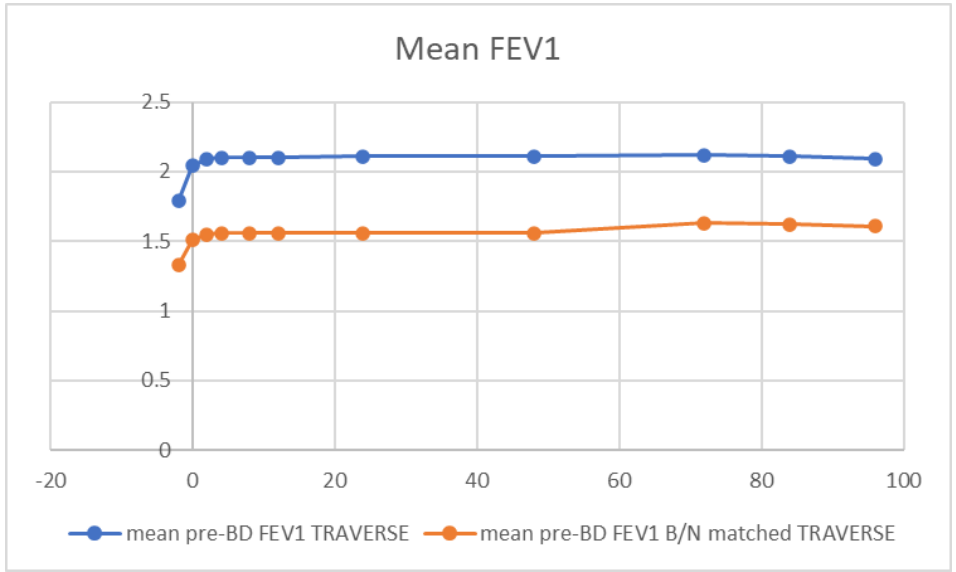
Key issue: Long-term treatment effect of dupilumab

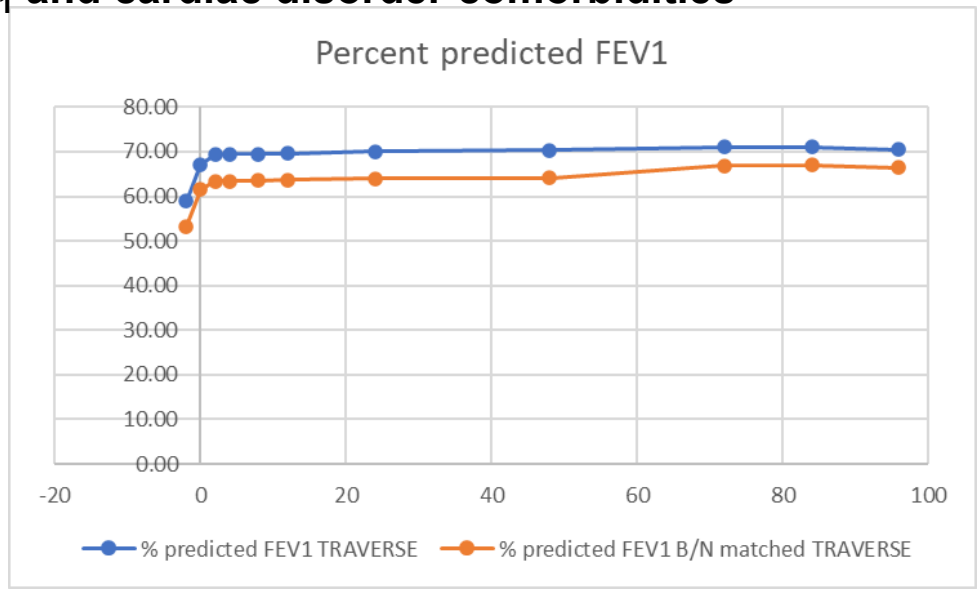
TRAVERSE population matched on age and pre-BD FEV_1





TRAVERSE population matched on age, pre-BD FEV_1 and cardiac disorder comorbidities



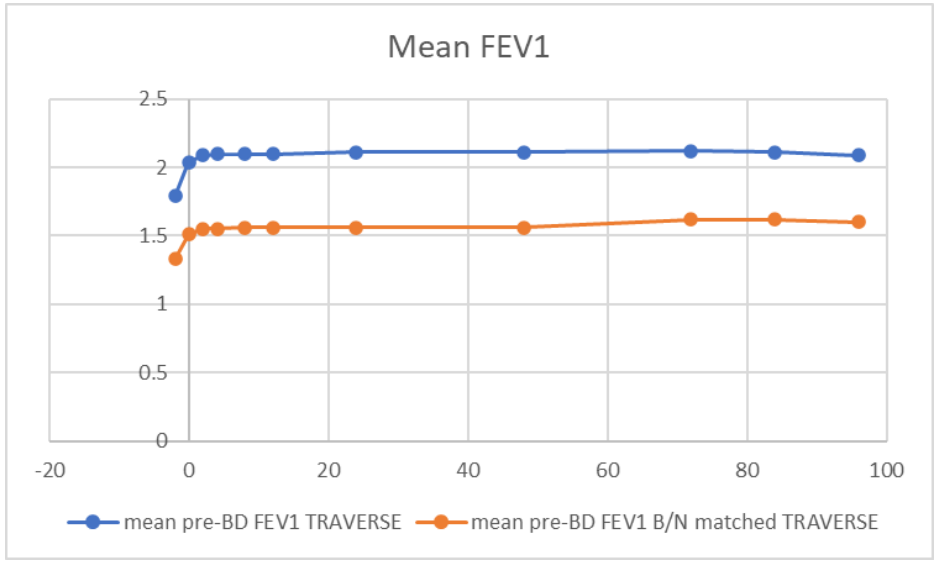


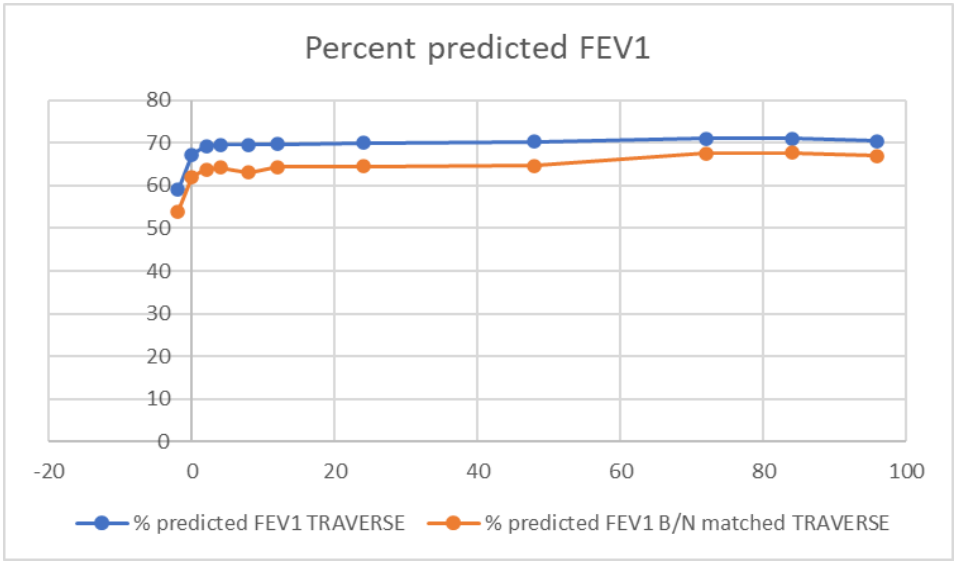
NICE

Key issue main deck

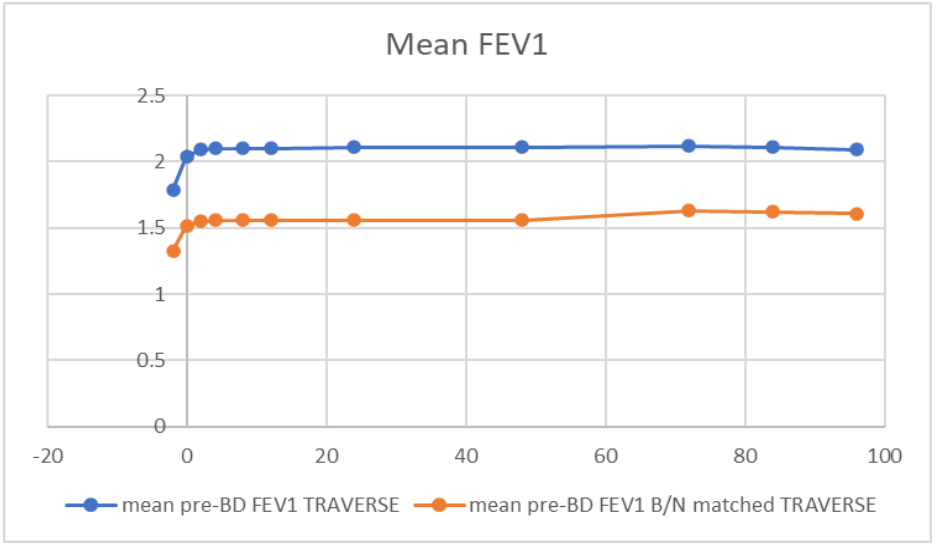
Key issue: Long-term treatment effect of dupilumab

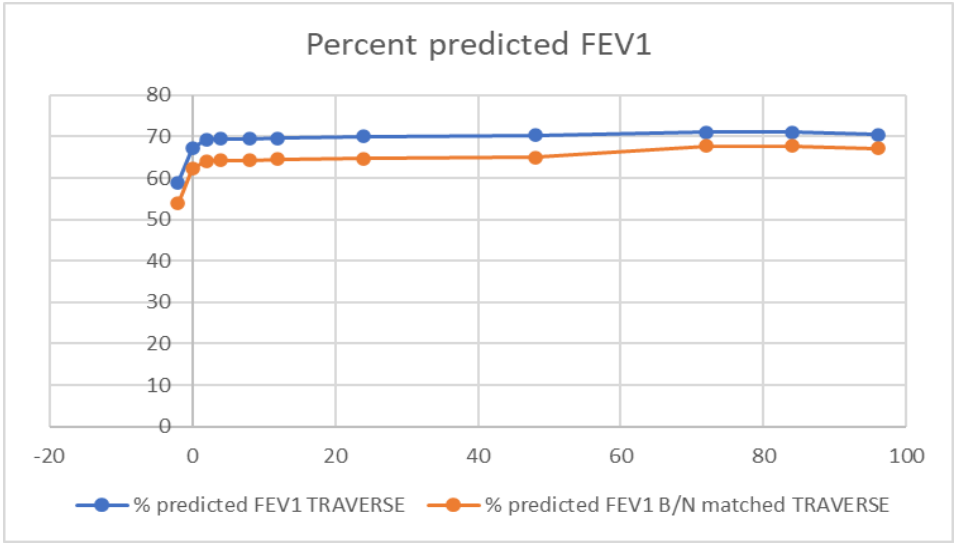
TRAVERSE population matched on age, pre-BD FEV_1 and vascular disorder comorbidities





TRAVERSE population matched on age, pre-BD FEV_1 and respiratory disorder comorbidities

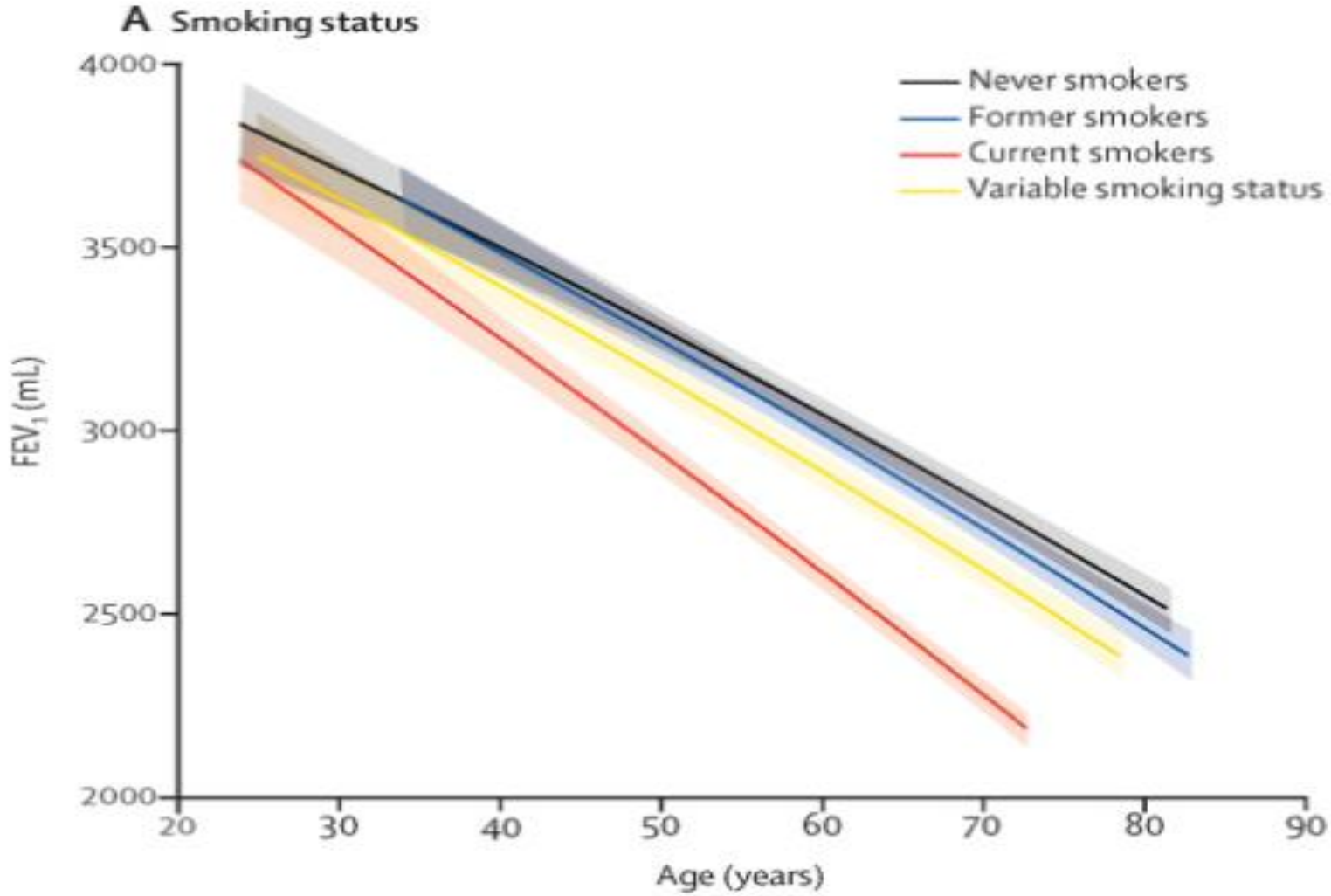




Key issue main deck

Key issue: Long-term treatment effect of dupilumab

Long term FEV_1 benefits of smoking cessation (Reproduced from Oelsner 2020)



Company base case results

Key issue main deck

Scenario analysis

ICERS at different CFRs between 10% and 40**% with NO background mortality (SMR) included** (model based on the updated draft guidance CEM base case)

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]

ICERS at different CFRs between 10% and 40% **with background mortality (SMR) included** (model based on the updated draft guidance CEM base case)

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]

CFR, case fatality rate; SMR, standardised mortality ratio; ICER, incremental cost effectiveness ratio; CEM, cost effectiveness model

Company base case results

Scenario analysis (2)

scenario analyses (deterministic; model based on the updated draft guidance CEM base case)

Scenario (applied to company base case)	Inc. costs (£) versus background therapy	Inc. QALYs versus background therapy	ICER (£/QALY) versus background therapy
Company base case	[redacted]	[redacted]	[redacted]
17.5% CFR (Echevaria 2017 and Echevaria 2022; 90 day survival) with SMR	[redacted]	[redacted]	[redacted]
29.8% CFR (Echevaria 2022; 1-year survival) without SMR	[redacted]	[redacted]	[redacted]
15.6% CFR (Hoogendoorn 2011) without SMR	[redacted]	[redacted]	[redacted]

COPD, Chronic obstructive pulmonary disease; CFR, case fatality rate; SMR, Standardised mortality ratio; ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year; CEM, cost effectiveness model

EAG base case results

Excess mortality

Scenario analysis (3)

scenario analyses (deterministic; applied to updated EAG base case)

Scenario (applied to company base case)	Inc. costs (£) versus background therapy	Inc. QALYs versus background therapy	ICER (£/QALY) versus background therapy	Median survival (years); dupilumab	Median survival (years); background therapy only
EAG base case (post ACM1)	[redacted]	[redacted]	[redacted]	10.2	9.0
Model start age of 69*	[redacted]	[redacted]	[redacted]	8.75	7.8
CFR of 17.5% based on Echevaria et al. with SMR	[redacted]	[redacted]	[redacted]	9.3	7.95
RR of trial primary outcome (0.69) used to inform all dupilumab exacerbations	[redacted]	[redacted]	[redacted]	10.2	9.0
RR for exacerbations modelled as per company base case, CFR of 11.9% and start age 69	[redacted]	[redacted]	[redacted]	9.2	7.8

*EAG notes that average age of patients in RWD presented by company was higher than start age in the model (based on trial data [age 65]).

CFR, case fatality rate; SMR, Standardised mortality ratio; ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year