Mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237]

For projector – confidential info redacted

Technology appraisal committee A [14 April 2026]

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Mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237]

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Background on chronic obstructive pulmonary disease (COPD)

COPD refers to a group of lung conditions that can cause breathing difficulties

Causes and epidemiology

- Key risk factors include smoking or long-term exposure to harmful fumes or dust
- Prevalence in England ~4.9% in adults ≥40 years and becomes more common with age

Symptoms and prognosis

- Common symptoms: shortness of breath, cough with phlegm, wheezing, chest tightness, difficulty exercising, and episodic flare-ups of respiratory symptoms, known as exacerbations
- COPD is a leading cause of death in England (47.3 deaths per 100,000 in 2023)

Diagnosis and classification

- Diagnosed based on clinical history, symptoms, and spirometry to assess airflow obstruction based on post-bronchodilator FEV_1 (graded 1-4, with 4 as the most severe)
- Around 20 to 40% have an eosinophilic phenotype (BEC ≥0.3 $x10^9$ cells/L) which is associated with raised risk of exacerbations

COPD, Chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in the first second; BEC, blood eosinophil count

Patient perspectives

People with COPD would welcome new, more effective treatments that improve QoL

Joint submission from Asthma + Lung UK and Taskforce for Lung Health, patient expert submission

- Breathlessness and other symptoms significantly impact ability to carry out everyday tasks and affect quality of life
- Impact on mental health → over 1 in 3 people with COPD report symptoms of anxiety and depression
- ICS prescribed for COPD can cause dry mouth, tremors, low bone density, oral infections and pneumonia → biologics such as mepolizumab may reduce ICS dose, potentially mitigating side effects
- Unmet need to reduce rate of exacerbations and lung function decline
- Travel to hospital every 4 weeks for mepolizumab may pose difficulties – home administration may reduce barriers to treatment

"I experience breathlessness daily, impacting my ability to do routine tasks. Many times, my breathlessness means I can't leave the house."

"The treatment that I'm on for my COPD doesn't feel to be particularly effective and every day I struggle with breathlessness."

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ICS, inhaled corticosteroids; COPD, Chronic obstructive pulmonary disease; QoL, quality of life

Clinical perspectives

Reducing exacerbations is a key treatment aim in current COPD care

Submissions from Association of Respiratory Nurses, clinical expert

- Main aims of treatment: reduce symptoms, prevent/treat exacerbations, and reduce disease progression and mortality risks
- Current care combines pharmacological treatment, self management, lifestyle and preventative measures – but consistency of implementing care pathway varies nationally
- Mepolizumab could offer a new and additional treatment in COPD management that reduces exacerbations and improves QoL
- Homecare delivery and self administration are likely to be available for mepolizumab

"The technology has the potential to reduce exacerbations…, therefore decreasing hospitalisations, emergency department visits, and urgent care attendances; while supporting more proactive and efficient disease management within existing NHS pathways."

COPD, Chronic obstructive pulmonary disease; QoL, quality of life

Equality considerations

Potential equality issues raised by company and in patient organisation submission

- **Deprivation**: People from socioeconomically deprived backgrounds are more likely to have COPD and have raised exacerbations, hospitalisation and mortality risks
    - Populations living in deprived areas are also more likely to have comorbidities that may affect COPD management
- **Access to care**: Variation in access to standard care for COPD and barriers to attending healthcare appointments may introduce inequalities based on geographical location

Are there any additional equality issues that need to be considered?

Mepolizumab (Nucala, GlaxoSmithKline)

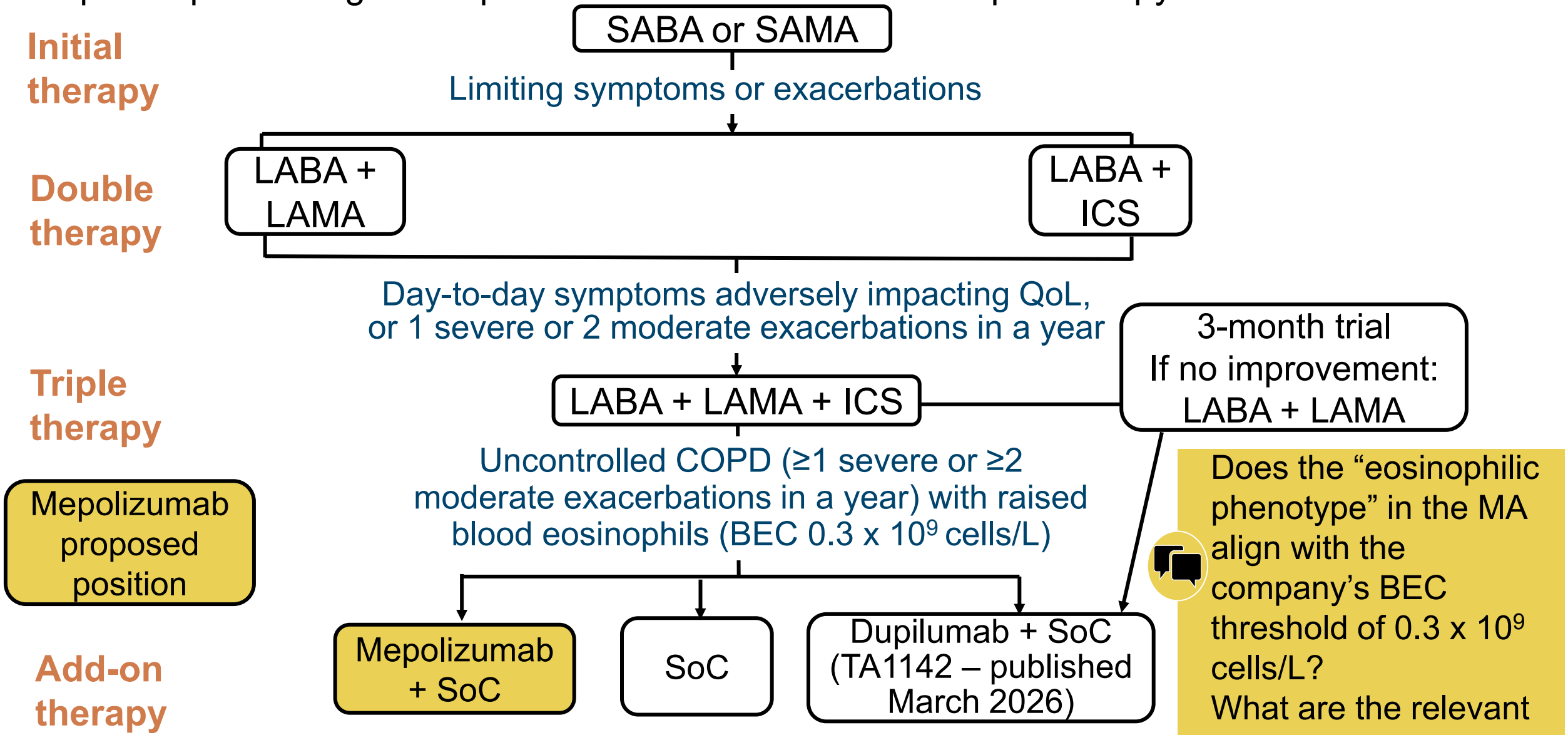
Marketing authorisation	• Indicated as add-on maintenance treatment for uncontrolled COPD of an eosinophilic phenotype on a combination of an inhaled corticosteroid (ICS), a long-acting beta-2 agonist (LABA), and a long-acting muscarinic antagonist (LAMA) • UK marketing authorisation granted December 2025
Mechanism of action	• Mepolizumab is a humanised IgG1κ monoclonal antibody specific for IL-5 • Inhibits IL-5 signalling, reducing the production and survival of eosinophils and eosinophilic-driven inflammation
Administration	• 100 mg administered subcutaneously once every 4 weeks
Price	• List price per pack: £840 per 100 mg dose • List price for 12 months of treatment: £10,958 • Agreed patient access scheme in place

Would mepolizumab be expected to be given at home? If so, what proportion would likely receive treatment at home?
Would home delivery be preferable for patients?
What proportion of people would be expected to self administer mepolizumab?

ICS, inhaled corticosteroids; COPD, Chronic obstructive pulmonary disease; QoL, quality of life; IL-5, interleukin 5 ; IgG; immunoglobulin G

Treatment pathway

Proposed positioning for mepolizumab is as an add-on to triple therapy



COPD, Chronic obstructive pulmonary disease; EOS, Eosinophils; ICS, Inhaled corticosteroids; LABA, Long-acting beta2- agonist; LAMA, Long-acting muscarinic antagonist; QoL, Quality of life; BEC, blood eosinophil count; SoC, standard of care; ACM, appraisal committee meeting; MA, marketing authorisation

Issues for discussion

Key issues	ICER impact
Comparative effectiveness of mepolizumab and dupilumab	Uncertain
Rates of moderate and severe exacerbations	Uncertain

Other issues	ICER impact
Generalisability	Uncertain
Use of dual therapy in baseline population	Uncertain

ICER, incremental cost effectiveness ratio

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Key mepolizumab clinical trials - MATINEE

3 clinical trials - MATINEE, METREX and METREO

METREX and METREO
COPD-HELP

	MATINEE
Design	Phase 3, multicentre, double-blind RCT
Population	Adults ≥40 years with moderate to very severe COPD (GOLD 2–4), BEC≥0.3 x10^9 cells/L at screening and historical BEC 0.15x10^9 cells/L in prior 12 months, ≥2 moderate exacerbations or ≥1 severe exacerbation in prior 12 months
Intervention and comparators	Mepolizumab (SC) 100 mg/mL (n=403) + SoC administered once every 4 weeks with SoC vs placebo with SoC (n=401)
Primary outcome	Annualised rate of moderate/severe exacerbations up to week 104
Key secondary outcomes	Time to first moderate/severe exacerbation, annualised rate of exacerbations requiring ED visit and/or hospitalisation, mortality, HRQoL, lung function

- Efficacy data based on pooled analysis of MATINEE plus a subset of METREX and METREO with BEC 0.3 x10^9 cells/L at screening (collectively termed the **pooled mITT-300** population)
- MATINEE study conducted 2019 to 2024 (during COVID-19 pandemic, see slide 18), METREO and METREX conducted pre-COVID
- Additional trial assessing mepolizumab (COPD-HELP) identified but not part of key evidence

COPD, Chronic obstructive pulmonary disease; GOLD; Global Initiative for Chronic Obstructive Lung Disease; BEC, blood eosinophil count; SC, subcutaneous; SoC, standard of care; ED, emergency department; HRQoL, health related quality of life; RCT, randomised controlled trial; mITT, modified intention to treat

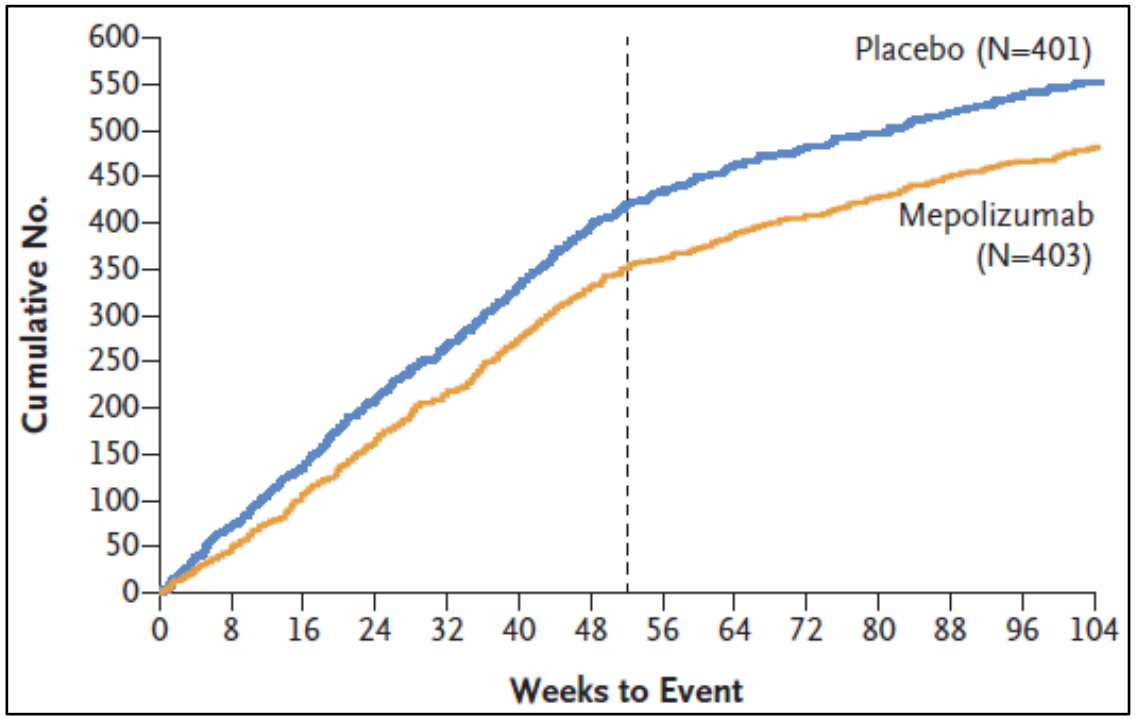
MATINEE and mITT-300 results: moderate or severe exacerbations

Mepolizumab resulted in a statistically significant reduction in annualised rate of moderate or severe exacerbations versus placebo in MATINEE, and the pooled mITT-300 population, up to 104 weeks

Annualised rate of moderate or severe exacerbations, MATINEE and pooled mITT-300 population

	Mepolizumab +SoC (95% CI)	Placebo + SoC (95% CI)
Adjusted annualised rate, MATINEE (Week 104 mITT)	0.80 (0.70, 0.91) (n=403)	1.01 (0.89, 1.15) (n=401)
RR, MATINEE	0.79 (0.66, 0.94); p=0.011	
Adjusted annualised rate, mITT-300 (52-104 week follow up)	[redacted] (n=568)	[redacted] (n=578)
RR, mITT-300	0.79 (0.68, 0.91); p=0.002	

Cumulative moderate or severe exacerbations, MATINEE



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COPD, Chronic obstructive pulmonary disease; CI, Confidence interval; BEC, blood eosinophil count; RR, rate ratio; mITT, modified intention to treat; SoC, standard of care

Participants in pooled mITT-300 population

METREO and METREX results

MATINEE and mITT-300 results: time to first moderate or severe exacerbation

Mepolizumab resulted in a statistically significant improvement in time to first moderate or severe exacerbation vs placebo in the MATINEE and pooled mITT-300 populations, up to 104 weeks

	MATINEE		Pooled mITT-300	
	Mepolizumab + SoC (n=403)	**Placebo + SoC (n=401)**	**Mepolizumab+ SoC (n=568)**	**Placebo+ SoC (n=578)**
Probability of exacerbation at Week 52 (95% CI)	46.1 (41.2, 51.2)	53.4 (48.5, 58.5)		
Probability of exacerbation at Week 104 (95% CI)	64.5 (57.5, 71.4)	68.3 (61.4, 74.9)		
HR (95% CI)	0.77 (0.64, 0.93); p=0.009			

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CI, confidence interval; HR, hazard ratio; mITT, modified intention to treat

MATINEE and mITT-300 results: severe exacerbations

Mepolizumab resulted in an improvement in the rate of severe exacerbations and time to first severe exacerbation versus placebo in the MATINEE and pooled mITT-300 populations, but these results were not statistically significant

	MATINEE		Pooled mITT-300	
	Mepolizumab + SoC (n=403)	**Placebo + SoC (n=401)**	**Mepolizumab+ SoC (n=568)**	**Placebo+ SoC (n=578)**
Participants with ≥1 severe exacerbation	11% (n=46)	15% (n=59)	[redacted]	[redacted]
Annualised rate of severe exacerbations	0.10	0.15	[redacted]	[redacted]
Severe exacerbations - RR (95% CI)	0.66 (0.43, 1.01); p=0.055		[redacted]	
Time to first severe exacerbation – HR (95% CI)	[redacted]		[redacted]	

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CI, confidence interval; HR, hazard ratio; mITT, modified intention to treat; RR, rate ratio

METREO and METREX results

Key issue: Comparative effectiveness of mepolizumab vs dupilumab (1)

ICER impact: **Uncertain**

Background

- Multiple ITCs (Bucher ITC, MAIC and ML-NMR) done to explore comparative effectiveness of mepolizumab and dupilumab – direction of effect varies depending on ITC method and how CB (key inclusion criteria for dupilumab trials) is defined
- MAIC uses adjusted mepolizumab trial populations to match dupilumab trials
- ML-NMR available for primary outcome only - requested at clarification due to low effective sample size of MAIC
- COPD-HELP (more severe population than other trials, see appendix) not included in ITCs

Company

- Company uses RRs to model treatment effect of mepolizumab versus dupilumab, based on the results of the MAIC where CB is defined by investigator assessment
- Investigator-assessed CB more closely matches method of outcome assessment in MATINEE than SGRQ-based assessments of CB – increases comparability across trials
- Baseline mean SGRQ scores higher in the restricted mepolizumab trial population, but closer in value to the dupilumab trial population with investigator-defined CB approach
- MAIC results suggest similar or larger benefit with mepolizumab vs dupilumab

ITC; indirect treatment comparison; CI, confidence interval; MAIC, matching adjusted indirect comparison; CB, chronic bronchitis; HRQoL, health related quality of life; ML-NMR; multi-level network meta-regression

=Favours mepolizumab

=Favours dupilumab

Indirect treatment comparison with dupilumab

When chronic bronchitis (CB) defined by investigator assessment, ML-NMR and MAIC results favour mepolizumab, Bucher ITC mostly favours dupilumab - CIs for all comparisons include 1

Outcomes when defining CB on investigator assessment (available for MATINEE only)	Bucher ITC, mepolizumab vs dupilumab	MAIC, mepolizumab vs dupilumab	ML-NMR, mepolizumab vs dupilumab
Annualised rate of moderate/severe exacerbations – RR (95% CI)	1.09 (0.78, 1.53)	0.91 (0.60, 1.37)	[redacted]
Annualised rate of severe exacerbations - RR (95% CI)	1.04 (0.47, 2.30)	0.68 (0.27, 1.72)	-
Time to 1st moderate or severe exacerbation - HR (95% CI)	0.93 (0.65, 1.32)	0.71 (0.46, 1.08)	-
SGRQ-C total score response, Week 52 – OR (95% CI)*	0.88 (0.53, 1.45)	1.19 (0.63, 2.24)	-

*Lower SGRQ-C score better

CI, confidence interval; HR, hazard ratio; RR, rate ratio; ITC; indirect treatment comparison; CI, confidence interval; MAIC, matching adjusted indirect comparison; SGRQ- St. George's Respiratory Questionnaire; ML-NMR, multi-level network meta-regression; OR, odds ratio

ITC methodology

=Favours mepolizumab

=Favours dupilumab

Indirect treatment comparison with dupilumab

When CB defined by SGRQ-C responses at baseline, results mostly favour dupilumab - CIs for all comparisons include 1

Outcomes when defining CB on SGRQ-C responses at baseline (pooled MATINEE, METREX and METREO)	Bucher ITC, mepolizumab vs dupilumab	MAIC, mepolizumab vs dupilumab	ML-NMR, mepolizumab vs dupilumab
Annualised rate of moderate/severe exacerbations – RR (95% CI)	1.09 (0.84, 1.41)	1.13 (0.80, 1.58)	[redacted]
Annualised rate of severe exacerbations - RR (95% CI)	1.02 (0.52, 1.99)	1.01 (0.47, 2.16)	-
Time to 1st moderate or severe exacerbation - HR (95% CI)	0.89 (0.67, 1.17)	0.71 (0.61,1.14)	-
SGRQ-C total score response, Week 52 - OR (95% CI)	0.97 (0.65, 1.46)	0.96 (0.58, 1.58)	-

*Lower SGRQ-C score better

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CI, confidence interval; HR, hazard ratio; ITC; indirect treatment comparison; MAIC, matching adjusted indirect comparison; SGRQ- St. George's Respiratory Questionnaire; OR, odds ratio; ML-NMR; multi-level network meta-regression

Key issue: Comparative effectiveness of mepolizumab vs dupilumab (2)

ICER impact: **Uncertain**

EAG comments

- MATINEE and dupilumab trials (BOREAS and NOTUS) used in the ITC took place during COVID-19 pandemic → likely fewer exacerbations during this time
  - Fewer exacerbations limits ability to demonstrate effectiveness of dupilumab → comparison may underestimate dupilumab effectiveness
- Pooled analysis breaks randomisation in METREX and METREO – no significant imbalances in baseline characteristics identified, but unreported factors may differ
- No evidence provided for whether proportional hazard assumption holds for comparison of mepolizumab vs dupilumab for time to first moderate/severe exacerbation – but outcome not used in modelling
- EAG overall opinion → ITC results suggest similar effectiveness of mepolizumab and dupilumab. But issues raised may contribute to uncertainty in results.

How should chronic bronchitis be defined for the indirect comparison?
Which indirect comparison is most suitable for decision making?
Has all the appropriate evidence been included in the ITCs (COPD-HELP excluded)?
Is it plausible to assume mepolizumab has a similar effectiveness profile to dupilumab?

MAIC, matching adjusted indirect comparison; ITC, indirect treatment comparison

Other issues: Generalisability

ICER impact: **Uncertain**

Background

- Current or historic uncontrolled comorbidities or unstable/life-threatening cardiac disease excluded from mepolizumab trials
- Significant proportion of people with COPD not currently being offered the five fundamentals of care as in NICE guideline 115, impacting efficacy of standard of care
- Higher baseline exacerbation rate results in a lower ICER (see appendix for baseline rates)

EAG comments

- Trial exclusion reasonable but uncertain how trial results may be applicable to broader COPD population with comorbidities that are eligible for mepolizumab
- Receipt of five fundamentals of care not reported across trials - may act as effect modifiers

Patient organisation submission

- Asthma + Lung UK 2025 survey – 8.8% of people with COPD report receiving all 5 fundamentals of care

Are the baseline characteristics sufficiently generalisable to people who would have mepolizumab in practice?
Are the results of the clinical trials sufficiently generalisable to the population eligible for mepolizumab?

COPD, chronic obstructive pulmonary disease; ICER, incremental cost effectiveness ratio

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Company's model overview

Model diagram

Company presented an exacerbation-based Markov model

Model structure

- Model includes states related to severity, frequency and time since exacerbations
  - Lung function decline not explicitly modelled
- 13 health states in model, plus 12 additional parallel discontinuation states for people stopping mepolizumab or dupilumab
- Frequent exacerbation states for people with >1 exacerbation within 12 months of first

EAG comments

- Mepolizumab affects QALYs by reducing the risk of moderate and severe exacerbations, which impact HRQoL – HRQoL improved in responders
- Mepolizumab affects costs through variations in % of people discontinuing mepolizumab, and changes in exacerbation rate
- Largest impacts on ICER are from changes in moderate and severe exacerbation rates, (with severe exacerbations having a greater impact), and age of population
- Modelling structure reasonable; some assumptions may increase structural uncertainty

How does lung function relate to exacerbation rate, the health states in the model (including time since exacerbation), and to cost and health outcomes?
Do the exacerbation-based health states sufficiently capture COPD outcomes?

QALY, quality-adjusted life year; HRQoL, health related quality of life; ICER, incremental cost effectiveness ratio

How company incorporated evidence into model

Input	Assumption and evidence source
Baseline characteristics	mITT-300 population of MATINEE, METREX, METREO, IMPACT and ECLIPSE studies (mean age 65.4 years, 31% female. 46.7% moderate COPD, 40.4% severe, 12.8% very severe (by FEV_1 predicted))
Treatment efficacy	Mepolizumab + SoC vs SoC alone: mITT-300 pooled analysis Mepolizumab + SoC vs dupilumab + SoC: RRs from MAIC
Utilities	EQ-5D data from pooled MATINEE, METREX, METREO and IMPACT studies, mapped to EQ-5D-3L where required
Time horizon	30 years (with 3-month model cycles)
Resource use	Based on NG115 COPD economic model (standard management and moderate exacerbations) and dupilumab (TA1142) model submission (severe exacerbations)
Stopping rule	After 52 weeks, only people responding to treatment continue mepolizumab and dupilumab

Should the recommendation include a stopping rule for mepolizumab?

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mITT, modified intention to treat; COPD, chronic obstructive pulmonary disease; FEV1, FEV1, forced expiratory volume in the first second; SoC, standard of care; RR, rate ratio; MAIC, matching adjusted indirect comparison; BNF, British National Formulary; NHS NCC, NHS National Cost Collection; PSSRU; Personal Social Services Research Unit

Treatment effect on exacerbations in model

Treatment effects	RR, moderate exacerbations (95% CI)	RR, severe exacerbations (95% CI)
Mepolizumab + SoC vs SoC alone	[redacted]	[redacted]
Mepolizumab + SoC vs SoC alone, responders* (week 52 onwards)	[redacted]	[redacted]
Mepolizumab + SoC vs dupilumab + SoC	0.91 (0.60, 1.37) (for moderate/severe exacerbations)	0.68 (0.27, 1.72)

* = Responders = fewer severe exacerbations than the year before, or an equal number of severe exacerbations and no increase in moderate exacerbations than the year before

- RR based on mITT-300 trial data for mepolizumab vs standard care and MAIC for mepolizumab vs dupilumab – moderate exacerbations for dupilumab calculated as function of total exacerbations risk minus risk of severe exacerbations
- Dupilumab responder treatment effect calculated by applying RRs from MAIC to mepolizumab responder exacerbation rates and adjusted for cycle length (responder RRs from dupilumab appraisal not publicly available)

CI, confidence interval; RR, rate ratio; MAIC, matching adjusted indirect comparison; SoC, standard of care

ICER impact: **Uncertain**

Key issue: Rates of moderate and severe exacerbations (1)

Background

- Mepolizumab trial primary endpoint was a combination of moderate or severe exacerbations, but in model the treatment effects on moderate and severe exacerbations are modelled separately
- RR for severe exacerbations based on small proportion of severe exacerbations during trials [redacted]

Committee conclusions and considerations in dupilumab appraisal

- Preferred to model reduction in moderate and severe exacerbations using rate ratio for combined moderate/severe exacerbations outcome, in line with primary trial outcome
- Exacerbation rates based on data with a low number of severe exacerbations (~10% of exacerbations across key trials) – size of reduction in severe exacerbations uncertain

RR, rate ratio; MAIC, matching-adjusted indirect comparison

Key issue: Rates of moderate and severe exacerbations (2)

ICER impact: **Uncertain**

Company

- Mepolizumab + SoC associated with statistically significant decrease in the rate of moderate exacerbations and strong numerical decrease in the rate of severe exacerbations versus SoC alone

EAG comments

- RR values are similar for moderate and severe exacerbations for mepolizumab + SoC vs SoC alone (moderate = [redacted], severe= [redacted]
  - Effect vs dupilumab + SoC: moderate/severe = 0.91 (95% CI 0.60, 1.37), severe = 0.68 (95% CI 0.27, 1.72)
- Modelled scenarios using same RR ([redacted]) for moderate and severe exacerbations vs SoC alone and moderate/severe RR (0.91) for moderate and severe exacerbations vs dupilumab - showed minimal changes in cost effectiveness results
- Also presented scenarios with RR=1 for severe exacerbations

What is the committee's preferred approach for modelling the rates of moderate and severe exacerbations – using a composite moderate/severe rate ratio for both moderate and severe exacerbations, or using separate rate ratios for each?

RR, rate ratio; MAIC, matching-adjusted indirect comparison; SoC, standard of care

Other issue: Use of dual therapy in baseline population

ICER impact: Uncertain

Background

- 2 studies - IMPACT and ECLIPSE - did not meet criteria to be included in treatment effect estimates, but were used to increase sample size in generating pooled population data to inform baseline patient characteristics, utility values (IMPACT only) and SoC exacerbation rates in model

EAG comments

- 61% of IMPACT population (34% in overall pooled baseline population) on dual therapy instead of triple therapy (required in mepolizumab MA)
- Since IMPACT showed smaller improvement with dual therapy than triple therapy, utility data calculated using this may be an underestimate of population utility
- Some issues with disutility values (see appendix) – disutility value at "Frequent severe (9-12 months)" health state smaller than "severe (9-12 months)" state
  - Alternative utility values have limited impact on ICER
- Overall, inclusion of ECLIPSE and IMPACT in pooled analyses is reasonable, but impact of potential study biases and including dual therapy patients should be considered

What impact does including people having dual therapy in the baseline population have on decision making?
Is including data from IMPACT and ECLIPSE in the model reasonable?

SoC, standard of care; MA, marketing authorisation

Summary of base case assumptions (1)

Company and EAG base cases align – no difference in preferred assumptions

Assumption	Company and EAG base case	Dupilumab appraisal – committee preference in similar evidence base
Model structure	Based on exacerbations (including time since exacerbation) – Lung function (GOLD stage) not modelled	Based on exacerbations and lung function as defined by GOLD status (accepted for decision making)
Rate ratios for exacerbations	Separate RRs for moderate and severe exacerbations	Pooled RRs for moderate and severe exacerbations
Stopping rule	52 weeks for non-responders	52 weeks for non-responders
Treatment effect after 52 weeks	No waning on exacerbation treatment effect. Increased responder-specific treatment effect after 52 weeks	No waning on exacerbation treatment effect. Increased responder-specific treatment effect after 52 weeks

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RR, rate ratio; GOLD; Global Initiative for Chronic Obstructive Lung Disease

Summary of base case assumptions (2)

Company and EAG base cases align – no difference in preferred assumptions

Assumption	Company and EAG base case	Dupilumab appraisal – committee preference in similar evidence base
Caregiver disutility	Excluded	Excluded
Utilities	EQ5D from MATINEE, METREX, METREO and IMPACT	Utility regression analysis to map to EQ5D
CFR for exacerbations	15.6% (Hoogendoorn et al. 2011)	14.2% (National Respiratory Audit Programme, 2021-23)
SMR for severe COPD	2.50 (Samyshkin et al. 2014)	2.33 for severe COPD, 4.1 for very severe (as defined by GOLD severity (Whittaker 2024)

CFR, case fatality rate; RR, rate ratio; SMR, standardised mortality rate; COPD, chronic obstructive pulmonary disease; GOLD; Global Initiative for Chronic Obstructive Lung Disease;

Cost effectiveness results

All ICERs are reported in Part 2 slides because they include confidential comparator discounts

- Base case ICERs (identical for company and EAG) are within the range NICE considers a cost-effective use of NHS resources for both mepolizumab + SoC vs SoC alone, and mepolizumab + SoC versus dupilumab + SoC
- Model parameters explored in Part 2 include scenarios around exacerbation rate, rate ratios for treatment effect, baseline utility and exacerbation disutility

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Uncaptured benefits

- Around 95% of people expected to self administer mepolizumab, which reduces administrative burden and barriers to accessing treatment
- Significant informal care required in COPD – the introduction of mepolizumab could benefit caregivers by decreasing the extent of informal care required. Caregiver disutility impact not currently captured in model

Are there any uncaptured benefits that should be considered in decision making?

COPD, chronic obstructive pulmonary disease

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Summary of issues

Key issues	ICER impact	Slide
Comparative effectiveness of mepolizumab and dupilumab	Uncertain	15-18
Rates of moderate and severe exacerbations	Uncertain	24-25

Other issues	ICER impact	Slide
Generalisability	Uncertain	19
Use of dual therapy in baseline population	Uncertain	26

Mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237]

Supplementary appendix

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Decision problem (1)

Population, intervention, comparators and outcomes from the scope

	Final scope	Company	EAG comments
Population	Adults with uncontrolled COPD with raised blood eosinophils (eosinophilic phenotype).	Adult patients with uncontrolled COPD (≥2 moderate or ≥1 severe exacerbations within 12 months) of an eosinophilic phenotype (BEC ≥0.3 x10^9 cells/L) on a combination of an ICS, a LABA, and a LAMA.	Appraisal population narrower than NICE final scope based on clinical trial criteria and use of triple inhaled therapy in line with MA. Severity defined by exacerbations instead of lung function as defined by GOLD staging
Intervention	Mepolizumab as an add-on to maintenance treatment.	As in NICE scope	Appropriate

BEC, blood eosinophil count; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; GOLD; Global Initiative for Chronic Obstructive Lung Disease

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Decision problem (2)

Population, intervention, comparators and outcomes from the scope

	Final scope	Company	EAG comments
Comparators	Standard care without mepolizumab Dupilumab with double or triple therapy (subject to NICE evaluation).	Standard care without mepolizumab (triple inhaled therapy). Dupilumab subject to NICE appraisal at time of CS.	Appropriate – no additional routinely used treatments. Dupilumab under NICE evaluation at time of EAG report submission.
Outcomes	Lung function, frequency of moderate or severe exacerbations, frequency of exacerbations resulting in hospital admission or ED visit, symptom control, mortality, AEs, HRQoL.	In line with NICE scope	Fewer outcomes available for comparison with dupilumab, but satisfied all key outcomes included.

CS, company submission; AE, adverse event; HRQoL, health related quality of life;

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Key clinical trials – METREX and METREO

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	METREX and METREO
Design	Phase 3, multicentre, double-blind RCT
Population	Adults ≥40 years with moderate to very severe COPD (GOLD 2–4), ≥2 moderate exacerbations or ≥1 severe exacerbation requiring hospital admission in prior 12 months. **METREO only**: BEC≥0.15x10^9 cells/L at screening or ≥0.3 x10^9 cells/L in prior 12 months)
Intervention and comparators	In subset for pooled analysis in appraisal: Mepolizumab (SC) 100 mg/mL administered Q4W with SoC vs placebo with SoC
Duration	52 weeks
Primary outcome	Annualised rate of moderate/severe exacerbations up to Week 52
Key secondary outcomes	Time to first moderate/severe exacerbation, annualised rate of exacerbations requiring ED visit and/or hospitalisation, mortality, HRQoL, lung function
Locations	METREX: 16 countries, no UK sites. METREO: 15 countries, including UK
Used in model?	Partly – subset of trial populations with BEC ≥0.3 x10^9 cells/L at screening

NICE

COPD, Chronic obstructive pulmonary disease; GOLD; Global Initiative for Chronic Obstructive Lung Disease; BEC, blood eosinophil count; SC, subcutaneous; SoC, standard of care; ED, emergency department; HRQoL, health related quality of life

Summary of participants in the pooled mITT-300 population

Study	mITT population		Pooled mITT-300 population	
	Mepolizumab + SoC, n (%)	Placebo + SoC, n (%)	Mepolizumab + SoC, n (%)	Placebo + SoC, n (%)
MATINEE	403 (39%)	401 (38%)	403 (71%)	401 (69%)
METREO	223 (21%)	226 (22%)	[redacted]	[redacted]
METREX	417 (40%)	419 (40%)	[redacted]	[redacted]
Total	1,043 (100%)	1,046 (100%)	568 (100%)	578 (100%)

Pooled mITT-300 criteria – all participants from MATINEE, plus participants from METREX and METREO with ≥0.3 x10^9 cells/L at screening who received ≥1 dose of study treatment and were on triple inhaled therapy (ICS+LABA+LAMA) at baseline

NICE

mITT, modified intention to treat; BEC, blood eosinophil count; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; SoC, standard of care

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COPD-HELP – trial population and results

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	Mepolizumab (n=119)	Placebo (n=119)
HR for median time to 1st readmission or death (all cause) - **primary endpoint**	HR 0.96 (0.70,1.32), p=0.811	
Moderate or severe exacerbations - RR (95% CI)	0.81 (0.66, 1.00)	
Adjusted annualised rate of severe exacerbations (95% CI)	1.65 (1.25, 2.05)	1.85 (1.42 to 2.29)
Severe exacerbations – RR (95% CI)	0.78 (0.51, 1.20)	
Adjusted annualised rate of moderate or severe exacerbations (95% CI)	2.80 (2.36, 3.23)	3.45 (2.94, 3.95)

- COPD-HELP population included adults ≥40 years admitted to hospital with acute exacerbations of COPD and BEC ≥0.3 x10^9 cells/L in prior 12 months, with treatment duration of 24 to 48 weeks
- Company did not include in efficacy estimates because COPD-HELP population had substantially more severe disease - including symptom burden (mean SGRQ-C 70.9 vs. 54.4 in mITT-300), CV comorbidity (35.7% vs 25% of mITT-300 population) and disease activity (5.3 exacerbations in the year before trial vs 2.4 in mITT-300 population)
- Company – mepolizumab showed a reduction in moderate/or severe exacerbations in COPD-HELP, consistent with MATINEE and mITT-300 pooled population results

NICE

COPD, Chronic obstructive pulmonary disease; BEC, blood eosinophil count; SoC, standard of care; ED, emergency department; SGRQ- St. George's Respiratory Questionnaire; CV, cardiovascular

METREX and METREO results: moderate or severe exacerbations

Mepolizumab resulted in a reduction in annualised rate of moderate or severe exacerbations and time to first exacerbation versus placebo in METREX and METREO at 52 weeks, but differences were statistically significant in the METREX mITT-300 subgroup only

	METREO, mITT-300 subgroup		METREX, mITT-300 subgroup	
	Mepolizumab + SoC (n=[redacted])	Placebo + SoC (n=[redacted])	Mepolizumab+ SoC (n=[redacted])	Placebo+ SoC (n=[redacted])
Annual exacerbation rate	[redacted]	[redacted]	[redacted]	[redacted]
RR, moderate or severe exacerbations (95% CI)	[redacted]		[redacted]	
Probability of exacerbation at week 52 (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR – time to first moderate or severe exacerbation (95% CI)	[redacted]		[redacted]	

CI, Confidence interval; RR, rate ratio; mITT, modified intention to treat; SoC, standard of care; HR, hazard ratio

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METREX and METREO results: severe exacerbations

Mepolizumab resulted in a reduction in annualised rate of severe exacerbations and time to first severe exacerbation versus placebo in METREX and METREO at 52 weeks, but differences were not statistically significant

	METREO, mITT-300 subgroup		METREX, mITT-300 subgroup	
	Mepolizumab + SoC (n=[redacted])	Placebo + SoC (n=[redacted])	Mepolizumab+ SoC (n=[redacted])	Placebo+ SoC (n=[redacted])
Participants with ≥1 severe exacerbation	[redacted]	[redacted]	[redacted]	[redacted]
Annualised rate of severe exacerbations (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
RR – severe exacerbations (95% CI)	[redacted]		[redacted]	
Probability of severe exacerbation, week 52 (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR – time to first severe exacerbation	[redacted]		[redacted]	

CI, Confidence interval; RR, rate ratio; mITT, modified intention to treat; SoC, standard of care; HR, hazard ratio

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MATINEE and mITT-300 results: SGRQ score

Mepolizumab resulted in a greater proportion of SGRQ responders and greater reduction (improvement) in SGRQ total score versus placebo in the MATINEE and pooled mITT-300 populations at 52 weeks, but relative risk of response is not statistically significant

	MATINEE		Pooled mITT-300	
	Mepolizumab (n=390)	**Placebo (n=393)**	**Mepolizumab (n=[redacted])**	**Placebo (n=[redacted])**
% responders (≥4-point improvement in SGRQ score) at week 52	50% (n=195)	46% (n=179)	[redacted]	[redacted]
LS mean change from baseline at week 52 (SE)	−8.0 (0.85)	−5.7 (0.85)	−7.1 (0.71)	−4.9 (0.70)
Difference, mepolizumab vs placebo (95% CI)	−2.3 (−4.64, 0.08); p=0.059		−2.2 (−4.14, −0.24); p=0.028	
Relative risk of response, mepolizumab vs placebo (95% CI)	1.04 (0.91, 1.20)		N/A	

NICE

SGRQ- St. George's Respiratory Questionnaire; LS, least squares; CI, confidence interval; SE, standard error

Indirect treatment comparison methodology

- Data used from mepolizumab vs placebo trials (MATINEE, METREO and METREX) and two dupilumab trials (NOTUS and BOREAS) for indirect comparison using placebo as common comparator
- To align with dupilumab trial criteria, people from mepolizumab trials were excluded from ITC if they did not have CB, had BEC <0.3 x10^9 cells/L at screening, mMRC score <2, or post-bronchodilator FEV_1 outside the moderate-severe range
- MAIC adjusted for age, sex, smoking status, eosinophil count, prior exacerbation history and QoL scores
    - ML-NMR (for primary trial outcome only) and unadjusted ITC also conducted
- Results for 2 populations produced based on definition of CB, defined either by investigator assessment at baseline (not available for METREO and METREX trials) or SGRQ-C responses at baseline (available for all mepolizumab trials)
    - ITC results used in model based on investigator-defined CB

BEC, blood eosinophil count; mMRC; FEV_1, forced expiratory volume in the first second; CB, chronic bronchitis; mMRC; Modified Medical Research Council; MAIC, matching adjusted indirect comparison; ITC, indirect treatment comparison

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Baseline exacerbation rates used in model

Source of baseline exacerbation	Rate of first moderate exacerbation (95% CI)	Rate of first severe exacerbation (95% CI)
Pooled trial analysis (post-randomization period (base case)	0.92 (0.85, 0.99)	0.17 (0.14, 0.20)
Calibrated so 1st year model prediction = baseline exacerbation rate in MATINEE for year before randomisation (scenario analysis)	1.58 (1.51, 1.66)	0.29 (0.25, 0.34)
METREX/METREO post-randomisation period (scenario analysis)	1.43 (1.19, 1.68)	0.20 (0.10, 0.29)

CI, confidence interval

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Disutility values used in model

State	Mean utility/disutility value	95% CI
No exacerbations – utility value	[redacted]	[redacted]
Moderate (0–3 months)		
Post-moderate		
Severe (0–3 months)		
Severe (3–6 months)		
Severe (6–9 months)		
Severe (9–12 months)		
Post-severe (>12 months)		
Frequent severe (0–3 months)		
Frequent severe (3–6 months)		
Frequent severe (6–9 months)		
Frequent severe (9–12 months)		

CI, confidence interval

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Company's model overview

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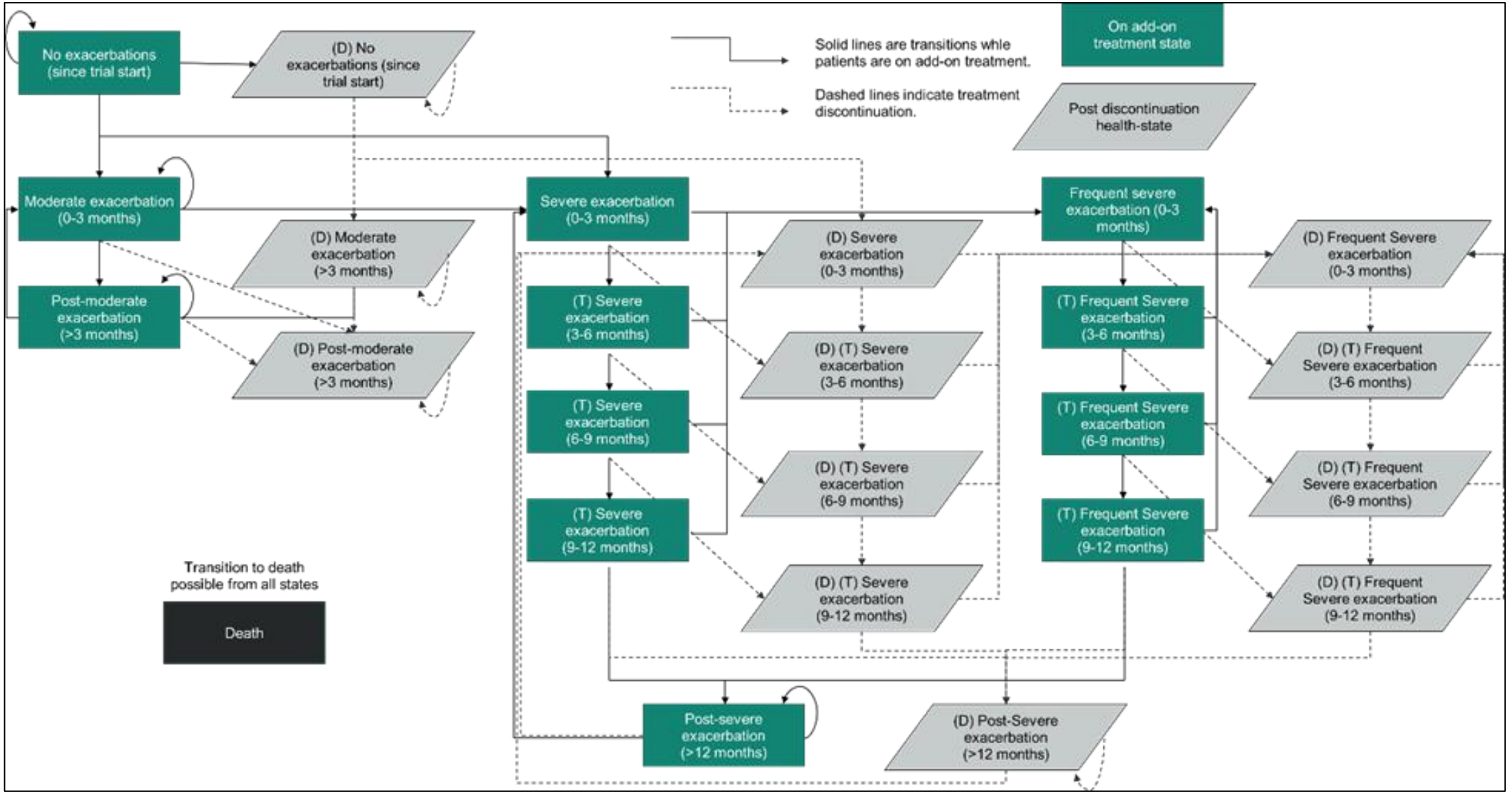
Company presented an exacerbation-based Markov model



Model parameters explored in scenario analysis

Model parameters	Assumption in base case
Source for baseline exacerbation rates	Pooled trial analysis (MATINEE, METREX, METREO) including IMPACT and ECLIPSE
Source of rate ratios for treatment effect	Mepolizumab + SoC vs SoC alone: mITT-300 pooled population Mepolizumab + SoC vs dupilumab + SoC: MAIC results where CB defined by investigator assessment
Source of Year 1 exacerbation rates	Pooled mITT-300 analysis
CFR for severe exacerbations	15.6% (Hoogendoorn et al. 2011)
Source of baseline utility	Pooled trial analysis (MATINEE, METREX, METREO), including the IMPACT trial
Source of exacerbation disutility	Pooled trial analysis (MATINEE, METREX, METREO), including the IMPACT trial

CFR, case fatality rate; mITT, modified intention to treat; CB, chronic bronchitis; MAIC, matching adjusted indirect comparison