

Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

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- 1. Company submission** from GlaxoSmithKline:
 - a. Full submission
 - b. Summary of Information for Patients (SIP)
 - c. Company submission addendum
- 2. Clarification questions and company responses**
 - a. Company's response to question A2
- 3. Patient group, professional group, and NHS organisation submission** from:
 - a. Asthma + Lung UK
 - b. Association of Respiratory Nurses (ARNS)
- 4. Expert personal perspectives** from:
 - a. Liam Knowles – Patient expert, nominated by Bridges Family and Carers Service
 - b. Richard Russel – Clinical expert, nominated by GSK
- 5. External Assessment Report** prepared by Newcastle University
 - a. EAG addendum
 - b. FAC to the EAG's addendum
- 6. External Assessment Group response to factual accuracy check of EAR**

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**NATIONAL INSTITUTE FOR HEALTH AND
CARE EXCELLENCE**

Single technology appraisal

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

Company evidence submission

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Table of contents

List of tables.....	5
List of figures	8
Abbreviations	9
Executive summary.....	12
1 Decision problem, description of the technology, and clinical care pathway	15
1.1 Decision problem	16
1.2 Description of the technology being evaluated	22
1.3 Health condition and position of the technology being evaluated	23
1.3.1 Disease overview	23
1.4 Epidemiology	26
1.4.1 Prevalence	26
1.4.2 Mortality	27
1.4.3 Disease burden	28
1.4.4 Clinical pathway of care	36
1.4.5 Unmet need.....	40
1.4.6 Positioning of mepolizumab.....	41
1.5 Equality considerations	43
2 Clinical effectiveness	45
2.1 Identification and selection of relevant studies	46
2.2 List of relevant clinical effectiveness evidence	48
2.3 Summary of methodology of the relevant clinical effectiveness evidence.....	55
2.3.1 Study methodology.....	55
2.3.2 Baseline characteristics.....	65
2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence	72
2.4.1 MATINEE	72
2.4.2 METREX and METREO	75
2.4.3 Pooled mITT-300 analysis (MATINEE [mITT], METREX [mITT-300] and METREO [mITT-300])	75
2.5 Critical appraisal of the relevant clinical effectiveness evidence.....	78
2.5.1 Applicability of trial populations to clinical practice in England	79
2.6 Clinical effectiveness results of the relevant studies.....	79
2.6.1 MATINEE	80
2.6.2 METREX and METREO	87
2.6.3 Pooled analysis of data from MATINEE mITT, METREO mITT-300 and METREX mITT-300 (pooled mITT-300 population)	87
2.7 Subsequent treatments used in the relevant studies	104
2.8 Subgroup analysis	104
2.8.1 MATINEE	104

2.8.2	METREX mITT-300 and METREO mITT-300.....	106
2.8.3	Pooled analysis of data from MATINEE mITT, METREO mITT-300 and METREX mITT-300 (pooled mITT-300 population).....	106
2.9	Meta-analysis.....	109
2.10	Indirect and mixed treatment comparisons.....	109
2.10.1	Brief description of the approach.....	109
2.10.2	Study population and setting.....	110
2.10.3	Evidence base.....	111
2.10.4	MAIC methodology.....	111
2.10.5	Matching variables.....	113
2.10.6	Calculation of weighted outcomes after matching.....	113
2.10.7	Results.....	115
2.10.8	Uncertainties in the indirect and mixed treatment comparison.....	126
2.11	Adverse reactions.....	127
2.11.1	MATINEE.....	127
2.11.2	METREX and METREO (safety population).....	130
2.12	Ongoing studies.....	132
2.13	Interpretation of clinical effectiveness and safety evidence.....	135
2.13.1	Comparison vs. standard of care.....	135
2.13.2	Comparison vs. dupilumab.....	137
2.13.3	Conclusions.....	137
3	Cost effectiveness.....	139
3.1	Published cost-effectiveness studies.....	140
3.2	Economic analysis.....	141
3.2.1	Patient population.....	143
3.2.2	Model structure.....	143
3.2.3	Intervention technology and comparators.....	150
3.3	Clinical parameters and variables.....	151
3.3.1	Patient characteristics.....	152
3.3.2	Responder rates.....	152
3.3.3	Exacerbation rates.....	153
3.3.4	Treatment discontinuation.....	158
3.3.5	Mortality.....	159
3.4	Measurement and valuation of health effects.....	161
3.4.1	Health-related quality of life data from clinical trials.....	161
3.4.2	Mapping.....	162
3.4.3	Health-related quality of life studies.....	162
3.4.4	Adverse reactions.....	166
3.4.5	Health-related quality of life data used in the cost-effectiveness analysis ...	166
3.5	Cost and healthcare resource use identification, measurement and valuation	168
3.5.1	Intervention and comparators' cost and resource use.....	168
3.5.2	Health-state unit costs and resource use.....	169
3.5.3	Adverse reaction unit costs and resource use.....	172

3.5.4	Miscellaneous unit costs and resource use	173
3.6	Severity.....	174
3.7	Uncertainty	174
3.8	Managed access proposal	175
3.9	Summary of base-case analysis inputs and assumptions	175
3.9.1	Summary of base-case analysis inputs	175
3.9.2	Assumptions.....	178
3.10	Base-case results	179
3.10.1	Base-case incremental cost-effectiveness analysis results.....	179
3.11	Exploring uncertainty	181
3.11.1	Probabilistic sensitivity analysis.....	181
3.11.2	Deterministic sensitivity analysis	183
3.11.3	Scenario analysis	187
3.12	Subgroup analysis	198
3.13	Benefits not captured in the QALY calculation	198
3.14	Validation.....	199
3.14.1	Validation of cost-effectiveness analysis	199
3.14.2	External Validation	200
3.15	Interpretation and conclusions of economic evidence	201
3.15.1	Strengths of the cost-effectiveness analysis.....	202
3.15.2	Limitations of the cost-effectiveness analysis	202
3.15.3	Conclusion	204
	References	206
	Appendices	227

List of tables

Table 1: The decision problem	18
Table 2: Technology being evaluated.....	22
Table 3: Population anticipated to be eligible for mepolizumab	27
Table 4: Summary of available clinical effectiveness evidence of mepolizumab	47
Table 5: Summary of clinical effectiveness evidence relevant to the decision problem.....	51
Table 6: Study design and methods	55
Table 7: Summary of participants in the pooled mITT-300 population	64
Table 8: MATINEE: Participant baseline characteristics (mITT population)	65
Table 9: Pooled mITT-300 population (MATINEE mITT + METREO mITT-300 + METREX mITT-300): Participant baseline characteristics	69
Table 10: Definition of analysis populations in the MATINEE trial	72
Table 11: Summary of statistical analyses in MATINEE	73
Table 12: Endpoints for pooled analysis of data from MATINEE mITT, METREX mITT-300, and METREO mITT-300 (pooled mITT-300 population).....	75
Table 13: Summary of statistical analyses in the pooled mITT-300 population.....	76
Table 14: Risk of bias assessment.....	78
Table 15: MATINEE: Primary endpoint – Annualised frequency of moderate/severe exacerbations (Week 104 mITT population).....	80
Table 16: MATINEE: Secondary endpoint – Time to first moderate or severe exacerbation (Week 104 mITT population).....	81
Table 17: MATINEE: Secondary endpoint – CAT score responders (Week 52 mITT population).....	82
Table 18: MATINEE: Secondary endpoint – SGRQ total score responders (Week 52 mITT population).....	83
Table 19: MATINEE: Secondary endpoint – E-RS:COPD score responders (Week 52 mITT population).....	84
Table 20: MATINEE: Secondary endpoint – annualised frequency of exacerbations requiring ED visit or hospitalisation (Week 104 mITT population)	84
Table 21: Summary additional efficacy and health outcomes endpoints from the MATINEE trial (mITT population)	85
Table 22: Pooled mITT-300 population (MATINEE mITT + METREO mITT-300 + METREX mITT-300): Annualised rate of moderate/severe exacerbations	87
Table 23: Pooled mITT-300 population (MATINEE mITT + METREO mITT-300 + METREX mITT-300): Time to first moderate or severe exacerbation.....	88
Table 24: Pooled mITT-300 population (MATINEE mITT + METREO mITT-300 + METREX mITT-300): Exacerbations requiring ED visit or hospitalisation.....	91
Table 25: Pooled mITT-300 population (MATINEE mITT + METREO mITT-300 + METREX mITT-300): Severe exacerbations	93
Table 26: Pooled mITT-300 population (MATINEE mITT + METREO mITT-300 + METREX mITT-300): CAT total score responders (Week 52).....	95
Table 27: Pooled mITT-300 population (MATINEE mITT + METREO mITT-300 + METREX mITT-300): Change from baseline in CAT score (Week 52).....	97

Table 28: Pooled mITT-300 population (MATINEE mITT + METREO mITT-300 + METREX mITT-300): SGRQ total score responders (Week 52).....	99
Table 29: Pooled mITT-300 population (MATINEE mITT + METREO mITT-300 + METREX mITT-300): Change from baseline in SGRQ-C score (Week 52).....	101
Table 30: Pooled mITT-300 population (MATINEE mITT + METREO mITT-300 + METREX mITT-300): SGRQ-C scores and change from baseline at Week 52	103
Table 31: Summary of subgroup analyses carried out on the primary endpoint (annualised rate of moderate/severe exacerbations) (pooled analysis of data from MATINEE, METREX mITT-300, and METREO mITT-300 [pooled mITT-300 population]).....	107
Table 32: Summary of sample sizes in the mepolizumab trials	116
Table 33: Baseline characteristics in combined BOREAS/NOTUS trials and restricted populations of the MATINEE mITT trial	117
Table 34: Baseline characteristics in the combined BOREAS / NOTUS trials and restricted populations of the pooled MATINEE / METREO / METREX trials	119
Table 35: ITC/MAIC estimates of mepolizumab vs. dupilumab.....	123
Table 36: Adverse events during or after the treatment period (safety population [†]).....	128
Table 37: MATINEE: Most common (≥5%) adverse events and most common (≥2%) serious adverse events on treatment (safety population).....	129
Table 38: MATINEE: Summary of on- and post-treatment pneumonia events (safety population)	129
Table 39: METREX and METREO: Overview of adverse events (safety population).....	130
Table 40: METREX and METREO: On-treatment AEs occurring in ≥5% patients (safety population)	131
Table 41: METREX and METREO: On-treatment and off-treatment pneumonia events (safety population)	132
Table 42: Summary overview of REALITI-C.....	133
Table 43: Health states included in the CEM.....	144
Table 44: Features of the economic analysis	148
Table 45: Background therapy weightings.....	150
Table 46: Clinical inputs available by study	151
Table 47: Population baseline characteristics used in the economic model.....	152
Table 48: Proportion of responders to mepolizumab and dupilumab used in the CEM	153
Table 49: Baseline exacerbation rates used in the model (base case).....	154
Table 50: Baseline exacerbation rates used in the model (scenario analysis)	154
Table 51: RRs for subsequent exacerbations.....	154
Table 52: Treatment effect for exacerbation rates, mepolizumab vs. background therapy (base case)	156
Table 53: Treatment effect for exacerbation rates, mepolizumab vs. background therapy (scenario analyses).....	156
Table 54: Treatment effect for exacerbation rates, mepolizumab vs. dupilumab	156
Table 55: RRs for exacerbations; responders (pooled mITT-300 population).....	157
Table 56: RRs for exacerbations; responders (MATINEE only).....	158
Table 57: Probability of discontinuation in Year 1, mepolizumab	158
Table 58: Probability of discontinuation in Year 2+	159
Table 59: Assessment of EQ-5D and data collected in proximity to exacerbation events ..	161

Table 60: Summary of studies reporting utilities for COPD exacerbation health states (NICE reference-case aligned subset)	164
Table 61: Summary of included studies that have developed or applied mapping methods to estimate EQ-5D utilities in COPD	165
Table 62: Summary of utility values for cost-effectiveness analysis.....	166
Table 63: Summary of disutility values for cost-effectiveness analysis: scenario analyses	168
Table 64: Drug acquisition costs for intervention and comparator treatments.....	169
Table 65: COPD management costs	170
Table 66: Moderate exacerbation resource use costs	171
Table 67: Severe exacerbation resource use costs	172
Table 68: Productivity loss model inputs	173
Table 69: Early retirement loss model inputs.....	174
Table 70: Summary of variables applied in the economic model	176
Table 71: Assumptions.....	178
Table 72: Base-case results (deterministic) – fully incremental analysis (mepolizumab PAS price).....	180
Table 73: Base-case results (probabilistic) (mepolizumab PAS price).....	182
Table 74: Key scenario analyses	187
Table 75: Scenario analysis results vs. SoC	189
Table 76: Scenario analysis results vs. dupilumab	190
Table 77: Features of the cost-comparison analysis	193
Table 78: Treatment discontinuation probabilities	194
Table 79: Treatment continuation probabilities	195
Table 80: Drug acquisition costs	195
Table 81: Administration costs	195
Table 82: Total administration costs.....	196
Table 83: Summary of model inputs.....	196
Table 84: Summary of key model assumptions	197
Table 85: Base-case results – mepolizumab PAS price	198
Table 86: Sensitivity analysis results – mepolizumab PAS price	198
Table 87: External validation of SoC model outcomes	200

List of figures

Figure 1: COPD pathophysiology	23
Figure 2: GOLD ABE assessment tool	25
Figure 3: GOLD 2025 stepwise pharmacological treatment of COPD	38
Figure 4: Current treatment pathway excluding mepolizumab	40
Figure 5: Proposed positioning of mepolizumab	43
Figure 6: Summary of clinical effectiveness evidence relevant to the decision problem	50
Figure 7: MATINEE study design schematic	56
Figure 8: Cumulative number of moderate or severe exacerbations.....	80
Figure 9: Cumulative incidence of first moderate or severe exacerbation (mITT)	82
Figure 10: Subgroup analyses (MATINEE): Primary endpoint (annualised rate of moderate/severe exacerbations up to Week 104)	105
Figure 11: Model schematic	144
Figure 12: Cost-effectiveness scatterplot of mepolizumab vs. dupilumab and SoC	183
Figure 13: Cost-effectiveness acceptability curve of mepolizumab vs. dupilumab and SoC	183
Figure 14: Tornado diagram of mepolizumab vs. SOC.....	185
Figure 15: Tornado diagram of mepolizumab vs. dupilumab	186
Figure 16: Cost-comparison model structure.....	193

Abbreviations

ACD	Appraisal Consultation Document
ACM	Appraisal Committee Meeting
AE	Adverse event
AESI	Adverse events of special interest
AMR	Antimicrobial resistance
BEC	Blood eosinophil count
BIA	Budget impact analysis
BMI	Body mass index
CAT	COPD Assessment Test
CB	Chronic bronchitis
CC	Cost-comparison
CCQ	COPD Control Questionnaire
CE	Cost-effectiveness
CFR	Case-fatality rate
CI	Confidence interval
CMA	Cost-minimisation analysis
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CPRD	Clinical Practice Research Datalink
CRSwNP	Chronic rhinosinusitis with nasal polyps
CUA	Cost-utility analysis
CV	Cardiovascular
DES	Discrete event simulation
EAG	External Assessment Group
ECG	Electrocardiogram
ED	Emergency department
EGPA	Eosinophilic granulomatosis with polyangiitis
E-RS:COPD	Evaluating Respiratory Symptoms in COPD
ESS	Effective sample size
EU	European Union
FeNO	Fractional exhaled nitric oxide
FEV ₁	Forced expiratory volume in one second
FPI-SF	Functional Performance Inventory-Short Form
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General practitioner

HCRU	Healthcare system resource use
HES	Hospital Episode Statistics
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICB	Integrated Care Board
ICS	Inhaled corticosteroid
IgG1κ	Immunoglobulin G, subclass 1, κ light chain
IL	Interleukin
ILC2	Innate lymphoid type 2
IPD	Individual patient data
IRR	Incidence rate ratio
ITC	Indirect treatment comparison
KM	Kaplan-Meier
LABA	Long-acting beta ₂ agonist
LAMA	Long-acting muscarinic antagonist
LRTI	Lower respiratory tract infections
LS	Least squares
MAIC	Matching adjusted indirect comparison
MAR	Missing at random
MCAR	Missing completely at random
MCID	Minimal clinically important difference
mITT	Modified intention-to-treat
mITT-300	Modified intention-to-treat 300 (participants with BEC ≥300 cells/μL at screening who received ≥1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline)
mMRC	Modified Medical Research Council
MMRM	Mixed model for repeated measures
MRC	Medical Research Council
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OR	Odds ratio
OWSA	One-way sensitivity analysis
POLI	Pharmaceutical Prices
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
Q2W	Every two weeks
Q4W	Every four weeks

QALY	Quality-adjusted life year
QOF	Quality and Outcomes Framework
QoL	Quality of life
QT	Interval on an electrocardiogram (ECG) representing the time between the start of ventricular depolarisation (Q wave) and the end of ventricular repolarisation (T wave)
RCT	Randomised controlled trial
RR	Rate ratio
RWE	Real-world evidence
SABA	Short-acting beta ₂ agonist
SAE	Serious adverse event
SAMA	Short-acting muscarinic antagonist
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SGRQ	St. George's Respiratory Questionnaire
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
T1	Type 1
T2	Type 2
T3	Type 3
Th2	T-helper type 2
TSD	Technical Support Document
UK	United Kingdom
US	United States
VAS	Visual analogue scale
WTP	Willingness-to-pay

Executive summary

Disease overview and burden

Chronic obstructive pulmonary disease (COPD) is a progressive inflammatory respiratory disease characterised by emphysema and/or chronic bronchitis (CB), leading to recurrent exacerbations, declining health status, and impaired quality of life (QoL). In England, ~1.2 million people had a recorded diagnosis of COPD in primary care in 2024/25 (1). Up to 40% of patients have Type 2 (T2) inflammation (eosinophilic phenotype; blood eosinophil count [BEC] ≥ 300 cells/ μ L) (2-7), which is associated with ~30% higher exacerbation risk (8) and 26% higher risk of all-cause mortality (9). Exacerbations are the main driver of disease progression, increased morbidity and mortality, and healthcare resource use (HCRU) (10-17), and contribute significantly to the £2 billion annual cost of COPD to the NHS (18).

Clinical pathway of care and unmet need

Triple inhaled therapy remains the current standard of care (SoC) for patients at high risk of exacerbations, supported by non-pharmacological and adjunctive measures (19). However, many people, particularly those with T2 inflammation, continue to exacerbate, and to date, no targeted biologic therapies have been recommended by the National Institute for Health and Care Excellence (NICE) in this population. Mepolizumab is proposed as an add-on maintenance treatment for adults with uncontrolled COPD (≥ 2 moderate or ≥ 1 severe exacerbations within 12 months) of an eosinophilic phenotype (BEC ≥ 300 cells/ μ L) on a combination of an inhaled corticosteroid (ICS), a long-acting beta₂ agonist (LABA), and a long-acting muscarinic antagonist (LAMA). While NICE guidance for the biologic dupilumab (20) is expected shortly, mepolizumab represents a similar, yet mechanistically distinct biologic option, directly targeting the interleukin IL-5 pathway rather than IL-4/IL-13 signalling to reduce exacerbations in patients with eosinophilic COPD.

Clinical effectiveness

Mepolizumab has been investigated in a broad population of patients with eosinophilic COPD, including patients with a wide spectrum of airflow obstructions (Global Initiative for Chronic Obstructive Lung Disease [GOLD] stages), COPD phenotypes, and the full range (0–4) of modified Medical Research Council (mMRC) dyspnoea scale grades (21-26). The Phase 3 programme includes three double-blind randomised controlled trials (MATINEE (21, 22), METREX (23, 24), and METREO (23, 25)) evaluating mepolizumab vs. placebo. MATINEE, the pivotal study for this submission, enrolled patients with eosinophilic COPD (BEC ≥ 300 cells/ μ L at screening and ≥ 150 cells/ μ L within the previous 12 months), and ≥ 2 moderate or ≥ 1 severe exacerbation(s) within the prior 12 months. A pooled analysis combined MATINEE data with patients with BEC ≥ 300 cells/ μ L from METREX and METREO, forming the pooled modified intention-to-treat (mITT)-300 population (27).

In MATINEE, mepolizumab significantly reduced the annualised rate of moderate/severe exacerbations by 21% vs. placebo (rate ratio [RR]: 0.79 [95% confidence interval (CI): 0.66, 0.94]; $p=0.011$), across a follow-up period of up to 2 years, delayed median time-to-first moderate/severe exacerbation by 98 days (hazard ratio [HR]: 0.77 [95% CI: 0.64, 0.93]; $p=0.009$), and reduced the annualised rate of exacerbations leading to emergency department (ED) visits and/or hospitalisations by 35%, which was nominally significant (RR: 0.65 [95% CI: 0.43, 0.96] (21, 22). Improvements in health-related quality of life (HRQoL) as measured by St. George's Respiratory Questionnaire for COPD patients (SGRQ-C) total scores over time vs. placebo, numerically favoured mepolizumab (-2.3 least squares [LS] mean difference; odds ratio for response of 1.17 at Week 52). No statistically significant differences were observed in COPD Assessment Test (CAT)/SGRQ-C/Evaluating Respiratory Symptoms (E-RS) outcomes vs. placebo (21, 22). Exacerbations were consistently reduced across GOLD Stages (2–4), COPD phenotypes, comorbidities, and disease duration (21, 22).

In the pooled mITT-300 population, results were consistent: mepolizumab significantly reduced the annualised rate of moderate/severe exacerbations (RR 0.79 [95% CI 0.68–0.91]; $p = 0.002$), lowered the probability of having a moderate/severe exacerbation (Week 104 HR: [REDACTED]), reduced ED/hospitalisation-related exacerbations (RR 0.71 [95% CI 0.51–0.98]; $p=0.03$ [nominally significant]), and resulted in a statistically significant improvement in SGRQ-C scores from baseline (-2.2 LS mean difference [95% CI: -4.14 , -0.24]; $p=0.028$) (27).

Given the evolving treatment landscape and the ongoing dupilumab NICE appraisal, with final guidance forthcoming (20), dupilumab would represent a relevant comparator for mepolizumab, should it receive a positive NICE recommendation. In the absence of head-to-head randomised controlled trials (RCT), a matching-adjusted indirect comparison (MAIC) was conducted to assess relative efficacy. After aligning RCT inclusion criteria and adjusting for baseline characteristics, no statistically significant differences were observed between treatments for the exacerbation and HRQoL outcomes analysed, however favourable numerical trends were observed for mepolizumab across various exacerbation outcomes. HRQoL improvements (SGRQ-C) were numerically similar between treatments. The MAIC excluded several mepolizumab subgroups (e.g., without CB, GOLD 4, and BEC <300 cells/ μ L) not eligible for the dupilumab trials, where mepolizumab demonstrated benefit vs placebo. In addition, mepolizumab is administered once every 4 weeks (Q4W) (28), compared with once every 2 weeks (Q2W) for dupilumab (29), potentially better suiting patient preferences for treatments with lower frequency of use (30) and reducing treatment burden and supporting adherence (31, 32).

Mepolizumab has an established safety profile across approved indications, studied for up to 10 years in both clinical trials and in the real world (33). The incidence of any adverse events (AE) and serious adverse events (SAE) was similar between mepolizumab- and

placebo-treated patients with COPD (23, 24, 34). The safety of mepolizumab in COPD is consistent with its known benefit:risk profile.

Cost-effectiveness

The economic analysis considers adult patients with uncontrolled COPD of an eosinophilic phenotype on a combination of an ICS, LABA, and a LAMA. Using the Patient Access Scheme price for mepolizumab, base-case results show that mepolizumab is associated with an incremental cost-effectiveness ratio (ICER) of £18,347 compared with SoC, which is below the £20,000 per quality-adjusted life year willingness-to-pay threshold. Dupilumab (at list price) is dominated by mepolizumab in the base-case pairwise analysis. Sensitivity/scenario analyses results are highly congruent with the deterministic analysis, with a probabilistic ICER of £18,383 vs. SoC. This is also true for 17 of the 19 scenario analyses performed for the comparison of mepolizumab with SoC, with the remaining two scenario analyses relating to the testing of shorter time horizons. At list price, dupilumab is dominated by mepolizumab across all but one of the scenario analyses (with mepolizumab still being cost-effective for the other scenario). Key model drivers from the one-way sensitivity analysis include factors impacting the baseline exacerbation rates for severe exacerbations, and mepolizumab treatment effect for severe exacerbations.

A cost-comparison scenario is also provided for the comparison of mepolizumab with dupilumab, given that the MAIC showed no statistically significant differences and either favourable or comparable numerical trends across all exacerbation outcomes for mepolizumab, indicating at least similar or greater health benefits. Over a 10-year time horizon, mepolizumab is associated with a cost-saving of £[REDACTED] when compared with the dupilumab list price.

Overall, the cost-effectiveness analysis demonstrates the potential for mepolizumab to be a well-tolerated, cost-effective addition to existing SoC in the NHS for patients with uncontrolled COPD with an eosinophilic phenotype, with three large, robust clinical trials demonstrating a significant reduction in exacerbations for patients receiving mepolizumab. The cost-effectiveness and cost-comparison analyses showed that mepolizumab is a less costly alternative when compared to the list price of dupilumab.

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

Disease overview and burden

- Chronic obstructive pulmonary disease (COPD) is a progressive inflammatory respiratory disease characterised by emphysema and/or chronic bronchitis (CB), with a complex and multifaceted burden due to symptoms, exacerbations, negative impact on quality of life (QoL), and decline in health status.
- A total of 1,207,974 people had a recorded diagnosis of COPD in primary care in England in 2024/2025, representing approximately 1.89% of the total population (1).
- Up to 40% of patients with COPD have evidence of Type 2 (T2) inflammation, presenting as an eosinophilic phenotype, defined by an elevated blood eosinophil count (BEC) of ≥ 300 cells/ μ L (2-7).
- This subgroup has a ~30% higher risk of exacerbations (8) and a 26% higher risk of all-cause mortality (9), despite triple therapy, which is comprised of inhaled corticosteroid (ICS) + long-acting beta₂-agonist (LABA) + long-acting muscarinic antagonist (LAMA).
- Exacerbations are characterised by acute worsening of dyspnoea (breathlessness), cough, or sputum, typically associated with systemic inflammation (10, 35). Exacerbations in COPD are the key driver of disease progression, increased morbidity and mortality, and healthcare resource use (HCRU) (10-16).
- Recurrent exacerbations and persistent symptoms lead to cumulative declines in QoL (13), with recovery often prolonged—around 20% of patients fail to return to their pre-exacerbation baseline within 8 weeks, and a proportion continue to show incomplete recovery at 3 months (10, 36, 37).
- Hospital outcomes following COPD exacerbation remain poor, with national audit data showing 7.5% mortality within 30 days, 14.2% within 90 days, and nearly 40% readmitted within 90 days of discharge, consistent with earlier European audit findings (38, 39).
- In the UK, annual National Health Service (NHS) spend on COPD was estimated at £2 billion in 2021, rising to £2.6 billion by 2040 (18). COPD exacerbations are the leading contributor to the overall economic burden of COPD (10). The estimated costs of managing moderate and severe exacerbations in England is expected to rise from £0.6 billion in 2011 to over £1 billion by 2030 (40).

Clinical pathway of care

- COPD care in England is delivered across a range of settings including primary, secondary, community, and acute care.
- The current standard of care (SoC) centres on inhaled pharmacological treatments, with triple therapy as the recommended maintenance regimen for patients at high risk of exacerbations, alongside non-pharmacological, adjunct, and supportive therapies.
- The emergence of biologic therapies represents a new treatment paradigm for patients with COPD. With dupilumab currently under appraisal by NICE (20), a positive recommendation would introduce a biologic therapy for patients with eosinophilic COPD (BEC ≥ 300 cells/ μ L), establishing a precedent for targeted approaches in this population.

Unmet need

- Despite current treatment pathways (including triple therapy), a significant proportion of patients with COPD, particularly those with evidence of T2 inflammation who have a higher risk of flare-ups) (3-7), continue to experience exacerbations.
- There are currently no targeted biologic therapies routinely available within the NHS. Given the elevated risk of exacerbations, mortality, and healthcare use in patients with T2 inflammation, there is a strong rationale and need for introducing new, mechanism-based treatments aimed specifically at this population.
- While guidance for the biologic dupilumab is forthcoming, mepolizumab represents a similar, yet mechanistically distinct biologic option, directly targeting the IL-5 pathway rather than IL-4/IL-13 signalling to reduce exacerbations in patients with eosinophilic COPD.

Proposed population for mepolizumab treatment

- The proposed positioning of mepolizumab in the treatment pathway would be as an add-on maintenance treatment for adult patients with uncontrolled COPD (defined as ≥ 2 moderate or ≥ 1 severe exacerbations within 12 months) of an eosinophilic phenotype (defined as BEC ≥ 300 cells/ μ L) on a combination of an ICS, a LABA, and a LAMA.

1.1 Decision problem

Mepolizumab (Nucala®) is indicated as an [REDACTED]

[REDACTED] (Appendix A). The decision problem for this submission defines eosinophilic phenotype as blood eosinophil count (BEC) ≥ 300 cells/ μ L and uncontrolled disease as ≥ 2 moderate or ≥ 1 severe exacerbation(s) in the previous year, aligned with the inclusion criteria of the MATINEE trial (21, 22).

Up to 40% of patients with COPD have evidence of Type 2 (T2) inflammation, presenting as an eosinophilic phenotype (BEC ≥ 300 cells/ μ L) (2-7), and this subgroup has a ~30% higher risk of exacerbations (acute worsening of symptoms (8)), which drive disease progression, significantly contribute to the clinical and economic burden of COPD, and have a substantial negative impact on patient quality of life (QoL) (Section 1.4.3).

The decision problem addressed in this submission is provided in Table 1, outlining any differences from the National Institute for Health and Care Excellence (NICE) final scope (41).

Note: At the time of submission, the NICE technology appraisal for dupilumab for maintenance treatment of uncontrolled COPD with raised blood eosinophils ID6235 is ongoing (20). The second appraisal committee meeting (ACM2) was held on 5 August 2025, and final guidance is pending. Given its inclusion in the final scope and the status of the NICE appraisal, with the possibility of imminent final guidance, a cost-comparison of mepolizumab vs. dupilumab has also been provided in this submission, as it represents a

relevant emerging comparator for mepolizumab. Whilst dupilumab use would be expected to increase over time, it is not yet established as routine standard of care (SoC), therefore comparison with optimised inhaled therapy remains important.

Table 1: The decision problem

	Final scope issued by NICE/reference case (41)	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with uncontrolled COPD with raised blood eosinophils (eosinophilic phenotype).	Adult patients with uncontrolled COPD (defined as ≥ 2 moderate or ≥ 1 severe exacerbations within 12 months) of an eosinophilic phenotype (BEC ≥ 300 cells/ μ L) on a combination of an ICS, a LABA, and a LAMA.	The NICE final scope covers all adults with uncontrolled COPD with raised blood eosinophils. The anticipated licence [REDACTED] This appraisal applies the MATINEE trial criteria: - Uncontrolled COPD (≥ 2 moderate or ≥ 1 severe exacerbation[s] in the prior year) despite triple therapy, and - Blood eosinophils ≥ 300 cells/μL at screening and ≥ 150 cells/μL in the prior year. The BEC ≥ 300 cells/μL threshold is recognised in COPD reports (e.g. GOLD 2025 (10)) as a reliable biomarker of treatment responsiveness, and biologic trials have shown greater and more clinically meaningful reductions in exacerbations in this subgroup (20-22, 42-44). Evidence is drawn from the overall MATINEE mITT population and the pooled mITT-300 population (MATINEE mITT plus the BEC ≥ 300 cells/μL at screening subgroups from METREX and METREO).
Intervention	Mepolizumab as an add-on to maintenance treatment.	In line with NICE scope.	NA.
Comparator(s)	- Standard care without mepolizumab - Dupilumab with double or triple therapy (subject to NICE evaluation).	Standard care without mepolizumab (triple inhaled therapy).	Patients with COPD who continue to experience exacerbations despite optimised inhaled therapy are typically managed with triple therapy (ICS/LABA/LAMA). There are currently no routinely available long-term treatment options beyond inhaled therapies. Roflumilast (TA461) and azithromycin may be considered only in selected cases but are not in scope for this appraisal (19, 45). Roflumilast (TA461) (45) is rarely used in UK clinical practice due to poor tolerability and safety concerns (real-world data indicate ~5% patients receive it (46)), and

	Final scope issued by NICE/reference case (41)	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			azithromycin used in infection-driven COPD, is limited by safety and monitoring requirements (19). Dupilumab (an IL-4/IL-13 inhibitor) is currently undergoing NICE appraisal as an add-on maintenance treatment for uncontrolled COPD with an eosinophilic phenotype, with final guidance imminent at the time of this submission. It therefore represents the most relevant emerging comparator for mepolizumab. While dupilumab is not yet established as routine SoC, comparison with optimised inhaled therapy remains important; however, dupilumab use is expected to increase over time, making cost-comparison vs. dupilumab a valid scenario.
Outcomes	• Lung function • Frequency of moderate or severe exacerbations • Frequency of exacerbations resulting in hospital admission or ED visit • Symptom control • Mortality • Adverse effects of treatment • HRQoL.	Outcomes are available in line with NICE scope.	All outcomes specified in the scope have been provided. However, the therapeutic value of biologic therapies in COPD lies in reducing exacerbations, which are clinically important events that significantly impair QoL, drive hospitalisations, and contribute to long-term disease progression (Section 1.4.3) (10, 42, 43). Exacerbation reduction is therefore a key treatment goal in eosinophilic COPD (44), reflecting both the clinical burden of the disease and the priorities of patients and clinicians. Severe exacerbations are a major driver of disease progression, mortality, and healthcare burden: a single severe event increases the risk of a subsequent exacerbation by 64% and the risk of death by 21% (47), with recurrent exacerbations compounding this risk further (15, 47). Among patients hospitalised for a severe COPD exacerbation, approximately 4–5% die during admission, and a further 9–11% die within 30 days of discharge, according to national data from the OHID. Around one-third (30–35%) of patients are readmitted or die within 90 days of discharge, reflecting the ongoing vulnerability of this population (17). These events also place a substantial burden on healthcare systems, accounting for up to 45% of total direct COPD costs (48).

	Final scope issued by NICE/reference case (41)	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	In line with NICE scope.	The core submission presents a CEA of mepolizumab vs. SoC, supported by evidence from MATINEE and the pooled mITT-300 analysis showing clinically meaningful reductions in exacerbations. However, as dupilumab is currently undergoing NICE appraisal (ACM2, 5 August 2025) for the maintenance treatment of uncontrolled COPD with raised blood eosinophils and final guidance release is imminent, the CEA also includes dupilumab as a comparator (focusing on the annualised rate of moderate/severe exacerbations). In addition, GSK believes a CC against dupilumab is relevant, given that the MAIC showed no statistically significant differences in exacerbation or HRQoL outcomes between treatments, indicating at least similar of greater health benefit. Notably, mepolizumab demonstrated numerically better efficacy compared with dupilumab for key exacerbation outcomes, including severe exacerbations in patients with investigator-defined chronic bronchitis. Accordingly, both CEA and CC scenarios are presented within this submission. The MAIC necessarily excluded several subgroups of patients enrolled in the mepolizumab programme (e.g. without chronic bronchitis, GOLD 4 disease, or BEC <300 cells/μL) that were not eligible for the dupilumab trials, however for these patients, benefit was demonstrated for mepolizumab vs. placebo and these data are used to inform the comparison of mepolizumab vs. SoC in the CEA.
Subgroups to be considered	If the evidence allows, the following subgroups of people may be considered: - Levels of eosinophils (at least 500 cells per microlitre) - Severity of COPD	Subgroup data are available in line with NICE scope.	Data for subgroups specified in the scope have been provided in Section 2.8.

	Final scope issued by NICE/reference case (41)	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	- Frequency of exacerbation within previous 12 months - Chronic bronchitis or not - Smoking status.		
Special considerations including issues related to equity or equality	NA.	- Higher disease burden: COPD disproportionately affects individuals from socioeconomically disadvantaged backgrounds compared with those from more advantaged groups. - Greater comorbidity load: These populations are more likely to have multiple co-existing health conditions, which can complicate management. - Increased exacerbation risk: Disadvantaged patients are at higher risk of frequent exacerbations and hospitalisations compared with those from less disadvantaged backgrounds.	While the NICE scope does not specify any equality or equity considerations, it is well established that COPD disproportionately affects individuals from socioeconomically disadvantaged backgrounds who also tend to have a higher comorbidity burden and consequently, are at higher risk of experiencing exacerbations and hospitalisations (49, 50). Given this, the potential for a well-tolerated and effective treatment to reduce exacerbations in this group is particularly important and relevant to NICE's commitment to reducing health inequalities. Including these considerations helps to ensure that the impact on underserved populations is appropriately reflected in this appraisal. Some patients may face barriers to attending healthcare appointments, including psychosocial and practical challenges (51). The potential to reduce these, through less frequent dosing, acknowledges and accommodates patterns of healthcare avoidance.

Abbreviations: ACM, Appraisal Committee Meeting; BEC, blood eosinophil count; CC, cost comparison; CEA, cost-effectiveness analysis; COPD, chronic obstructive pulmonary disease; ED, emergency department; GOLD, Global Initiative for Chronic Obstructive Lung disease; HRQoL, health-related quality of life; ICS, inhaled corticosteroid; IL-4, interleukin-4; IL-13, interleukin-13; LABA, long-acting beta₂-agonist; LAMA, long-acting muscarinic antagonist; MAIC, matching-adjusted indirect comparison; mITT, modified intention-to-treat; NA, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OHID, Office for Health Improvement and Disparities; PSS, Personal Social Services; QALY, quality-adjusted life year; QoL, quality of life; SoC, standard of care; TA, technology appraisal; UK, United Kingdom.

1.2 Description of the technology being evaluated

The draft summary of product characteristics (SmPC) and the United Kingdom (UK) public assessment report are provided in Appendix A.

A description of mepolizumab is provided in Table 2.

Table 2: Technology being evaluated

UK approved name and brand name	Mepolizumab (Nucala®)
Mechanism of action	Mepolizumab is a humanised monoclonal antibody (IgG1κ), which targets human IL-5 with high affinity and specificity (52). IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation and survival of eosinophils (52). Mepolizumab inhibits the bioactivity of IL-5 with nanomolar potency by blocking the binding of IL-5 to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface, thereby inhibiting IL-5 signalling and reducing the production and survival of eosinophils (53).
Marketing authorisation/CE mark status	Mepolizumab does not yet have marketing authorisation for the indication in this submission. A regulatory submission was made to the MHRA in 02/2025 via the MHRA national procedure, with approval expected 01/2026. CHMP positive opinion is expected 01/2026, and EU regulatory approval in 03/2026.
Indications and any restriction(s) as described in the SmPC	Mepolizumab is anticipated to be indicated for use [REDACTED] (Appendix A). Contraindications: Hypersensitivity to the active substance or to any of the excipients (sucrose, sodium phosphate dibasic heptahydrate, citric acid monohydrate, polysorbate 80, disodium edetate, water for injections) (Appendix A).
Method of administration and dosage	The recommended dose of mepolizumab for adult patients with COPD with an eosinophilic phenotype is 100 mg administered SC Q4W (Appendix A).
Additional tests or investigations	Not required.
List price and average cost of a course of treatment	The list price of mepolizumab is £840 per 100 mg dose. The average cost of a course of treatment per patient per year is £10,958.
PAS (if applicable)	A confidential PAS discount of [REDACTED]% is in place, resulting in a net price of £[REDACTED] per 100 mg per 1 mL solution.

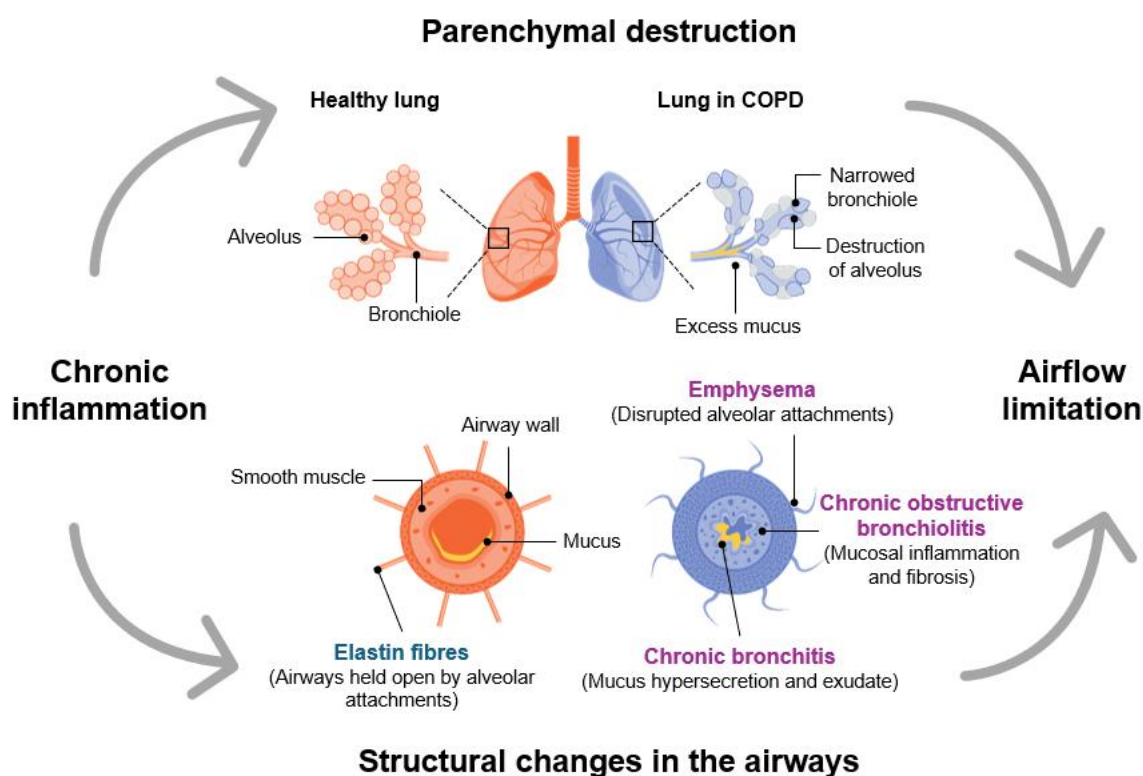
Abbreviations: CHMP, Committee for Medicinal Products for Human Use; COPD, chronic obstructive pulmonary disease; EU, European Union; ICS, inhaled corticosteroid; IgG1κ, immunoglobulin G1 kappa; IL-5, interleukin-5; LABA, long-acting beta₂-agonist; LAMA, long-acting muscarinic antagonist; MHRA, Medicines and Healthcare products Regulatory Agency; PAS, patient access scheme; Q4W, every 4 weeks; SC, subcutaneous; SmPC, summary of product characteristics.

1.3 Health condition and position of the technology being evaluated

1.3.1 Disease overview

COPD is a heterogeneous disease characterised by chronic respiratory symptoms (such as dyspnoea [breathlessness], cough with phlegm, frequent chest infections and persistent wheezing), and recurrent exacerbations (Section 1.3.1.1) resulting from structural and functional abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) causing persistent airway obstruction (Figure 1) (10, 54). Chronic inflammation drives airway remodelling, mucus hypersecretion, airflow limitation, and ultimately gas trapping and subsequent lung hyperinflation (10, 54), leading to progressive decline in lung function and health status, repeated exacerbations, and cumulative tissue damage that worsens prognosis; and, in severe or advanced cases, leads to disability and death (10).

Figure 1: COPD pathophysiology



Source: Barnes 2015 (54, 55); GOLD 2024 (1, 54)

Abbreviations: COPD, chronic obstructive pulmonary disease.

1.3.1.1 COPD exacerbations

COPD exacerbations are defined as acute episodes of worsened respiratory symptoms, beyond normal daily symptom variation. Exacerbations are the key driver of disease progression, increased morbidity and mortality, and healthcare resource use (HCRU) (10-12), resulting in a significant clinical and economic burden. Exacerbations significantly and

Company evidence submission for mepolizumab for treating chronic obstructive pulmonary disease with an eosinophilic phenotype [ID1237]

cumulatively impair patients' quality of life (QoL), leading to functional loss, worse health status, and prolonged recovery periods, with QoL seldom returning to pre-exacerbations levels (Section 1.4.3).

1.3.1.2 Inflammatory pathways and biomarkers in COPD

COPD has both distinct and overlapping inflammatory pathways, categorised into Type 1 (T1), Type 2 (T2), and Type 3 (T3) endotypes (56-58), which have different gene expression signatures, cytokine activation, source and effector cells, and clinical features (19, 57, 59-62).

T2 inflammation, which presents as eosinophilic COPD, is driven by the release of epithelial cytokines such as IL-33, which activate T-helper type 2 (Th2) and innate lymphoid type 2 (ILC2) cells (61, 63, 64) to release the T2 cytokines IL-4, IL-5, and IL-13, stimulating eosinophil production and effecting their recruitment to the lungs (65). IL-5 plays a central role in both stable disease and during exacerbations, mediating inflammation via the adaptive and innate immune response (56, 61, 66-71). Recent evidence shows IL-5 has broad, multidirectional effects on ten immune and structural cells (67, 68, 72, 73) and its dysregulation contributes to various pathophysiological processes, including mucus plugging (73, 74). IL-5 levels are elevated in the serum and sputum of patients with moderate-to-severe COPD (75), and higher IL-5 levels are correlated with greater COPD severity in some patients (75, 76).

T2 cytokines promote several other downstream pathological processes, including airway remodelling, goblet cell hyperplasia, epithelial barrier dysfunction, and mucociliary impairment and mucus hypersecretion (62). These features are particularly pronounced in patients with raised BEC, who represent a distinct subgroup with increased exacerbation risk, more rapid lung function decline, and greater HCRU. The ≥ 300 cells/ μ L cut-off is recognised in COPD reports (e.g. the Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2025 report (10)) as predictive of response to inhaled corticosteroids (ICS) and, by extension, to biologics targeting eosinophilic inflammation. At ≥ 300 cells/ μ L, eosinophilic activity is more persistent, increasing its reliability as a biomarker of treatment responsiveness. Clinical trials of biologics have demonstrated consistent and clinically meaningful reductions in exacerbation frequency in this subgroup (10, 20-22, 42-44).

1.3.1.3 COPD diagnosis and assessment

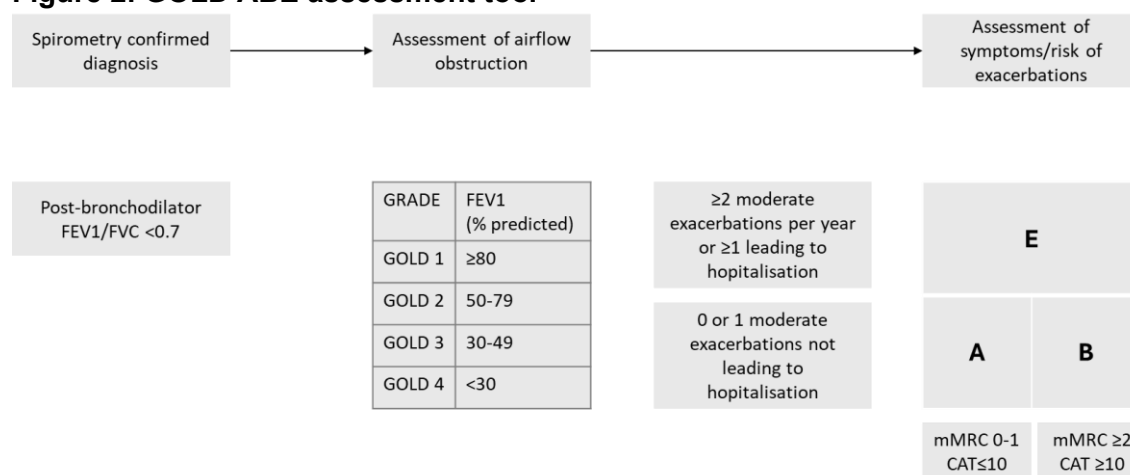
According to the GOLD 2025 Global Strategy for the Diagnosis, Management, and Prevention of COPD report (10) and NICE guidelines for the diagnosis and management of COPD in people ≥ 16 years of age (19), a COPD diagnosis may be considered based on the presence of risk factors or symptoms including; progressive, persistent dyspnoea that is worse with exercise, recurrent wheeze, chronic cough that may be intermittent or that may be productive, and recurrent lower respiratory tract infections (LRTI; bronchitis).

Company evidence submission for mepolizumab for treating chronic obstructive pulmonary disease with an eosinophilic phenotype [ID1237]

It is typically diagnosed in primary care, based on a combination of clinical history, symptom profile, risk factors (notably smoking), and confirmation of airflow limitation via spirometry. A post-bronchodilator forced expiratory volume in 1 second/ forced vital capacity (FEV₁/FVC) ratio of <0.7 confirms the presence of persistent airflow obstruction, consistent with COPD (10). The severity of airflow obstruction is classified into four grades, based on post-bronchodilator FEV₁, with Grade 4 being the most severe (FEV₁ <30% of predicted).

GOLD developed the ABE assessment tool (10), which recognises the importance of exacerbations alongside symptom burden and airflow obstruction, classifying patients into one of three lettered groups (A, B, or E; Figure 2), in order to recommend appropriate initial treatments. Patients in GOLD group E (with an exacerbation history of ≥2 moderate exacerbations or ≥1 severe exacerbation in 12 months) may be considered to have a worse prognosis and broadly represent the target population for this submission.

Figure 2: GOLD ABE assessment tool



Source: GOLD, 2025 (10)

Abbreviations: CAT, COPD Assessment Test; FEV, forced expiratory volume; COPD, chronic obstructive pulmonary disease; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council.

Following diagnosis, ongoing clinical assessment is essential to determine disease severity, guide treatment, and monitor progression. This includes:

- Symptom evaluation using validated tools such as the Modified Medical Research Council (mMRC) dyspnoea scale or the COPD Assessment Test (CAT) (19). For the assessment of symptom burden beyond the “ABE” classification, GOLD recommends the use of multidimensional questionnaires such as the CAT, COPD Control Questionnaire (CCQ), mMRC dyspnoea scale and St. George’s Respiratory Questionnaire (SGRQ) (10).

- Exacerbation history, including frequency and severity in the previous 12 months. The severity of exacerbations is classified most simply by GOLD (10) and NICE (19) based on the level of treatment required.
- Assessment of comorbidities, which are common and can significantly impact outcomes. Prognostic indicators for COPD are summarised in the recently updated NICE Clinical Knowledge Summary for COPD (77), highlighting severity of airflow obstruction, smoking status, severity of symptoms, chronic hypoxia and/or cor pulmonale, low body mass index (BMI), frequency and severity of exacerbations, hospital admission, multimorbidity and frailty.

While there is not a specific diagnosis of eosinophilic COPD given by GOLD, it recognises BEC as a validated biomarker of T2 inflammation (10). BEC is widely available and routinely used in UK clinical practice to guide treatment escalation (19), including the use of triple therapy and identification of patients who may benefit from biologics. BEC ≥ 300 cells/ μ L is associated with a higher risk of exacerbations, accelerated lung function decline, and greater likelihood of response to ICS or targeted therapies (10). The threshold is therefore used to define the target population for this submission.

1.4 Epidemiology

1.4.1 Prevalence

According to the 2024/2025 Quality and Outcomes Framework (QOF) (1), 1,207,974 people had a recorded diagnosis of COPD in primary care in England, representing approximately 1.89% of the total population in England and the most recent national estimate of diagnosed prevalence. Another, large population-based study using linked Clinical Practice Research Datalink (CPRD Aurum) and Hospital Episode Statistics (HES) data estimated that the point prevalence of diagnosed COPD among adults aged ≥ 40 years was 4.9% in 2019, with prevalence increasing steadily over the preceding two decades (78). This study also estimated that approximately 500,000 people in England were living with undiagnosed COPD in 2019.

Within the broader COPD population, a substantial proportion, estimated at around 20–40%, exhibit T2 inflammation (3-7, 79), typically characterised by elevated BEC.

The estimated number of patients eligible for mepolizumab treatment in England was calculated using the published 2024/25 QOF prevalence data (1,207,974 people living with COPD in England; Table 3) (1). Around 40% of these patients are estimated to experience ≥ 2 moderate exacerbation(s) or ≥ 1 severe or annually (80). However, as highlighted in the dupilumab NICE appraisal, moderate exacerbations are frequently self-managed with rescue packs, and therefore often go unreported in real world practice (20). Consequently, it is

assumed patients eligible for mepolizumab are unlikely to be identified unless they present to the hospital with a moderate or severe exacerbation while already receiving optimal (triple) inhaled therapy (20).

On this basis, the analysis focuses on patients with hospitalised exacerbations. According to HES England 2022/23 data reported in the dupilumab appraisal, 7.6% of patients with COPD had a non-elective hospitalisation (20), equating to ~91,806 individuals. Of these, Whittaker *et al.*, 2022, reported that among patients >40 years of age registered at UK general practices, 39.3% with ≥ 1 severe exacerbations were already on triple therapy (81), corresponding to 36,080 patients. Finally, as studies have shown that T2 inflammation, defined by a BEC ≥ 300 cells/ μ L, occurs in up to 40% of patients with COPD (3-7), the estimated eligible population in England for mepolizumab is 14,432 patients.

Table 3: Population anticipated to be eligible for mepolizumab

	Statistic	Source	Calculated value
Registered patients with COPD in primary care	1,207,974	QOF 24/25 (1)	1,207,974
Patients treated with triple therapy	39.3%	Whittaker <i>et al.</i> , 2022 (81)	474,733
Uncontrolled patient with ≥ 1 exacerbation requiring hospitalisation	7.6%	HES 2022/23 as reported in dupilumab appraisal (20)	36,080
Patients with raised eosinophils (BEC ≥ 300 cells/ μ L)	40%	Published sources (3-7, 79), in line with dupilumab appraisal (20)	14,432 patients estimated to be eligible for mepolizumab

Abbreviations: BEC, blood eosinophil count; COPD, chronic obstructive pulmonary disease; HES, Hospital Episode Statistics; QoF, Quality and Outcomes Framework.

1.4.2 Mortality

COPD remains a leading cause of death in the UK. According to the Office for Health Improvement and Disparities (OHID) Respiratory Disease Profile, the age-standardised mortality rate for COPD in England was 47.3 deaths per 100,000 population in 2023, with a 3-year rolling average of 43.9 deaths per 100,000 (2021 to 2023) (17). Mortality rates are substantially higher in more deprived areas, where people in the most deprived decile experience almost double the rate compared with those in the least deprived decile (17). Regional variation is also pronounced, with the highest rates observed in the North East and North West of England, reflecting socioeconomic disparities in disease prevalence, access to care, and early diagnosis (17).

Outcomes following COPD exacerbations remain poor despite improvements in acute and post-acute management. In a European COPD audit, which included more than 16,000 hospital admissions across 13 countries including the UK, in-hospital mortality was 4.3%, with 15% of patients dying and 35% readmitted within 90 days of discharge (38). More recent

national data from the Royal College of Physicians National Respiratory Audit Programme (NRAP) show that among 89,945 adults admitted to hospital in England and Wales for an exacerbation of COPD between 2021 and 2023, 7.5 % died within 30 days and 14.2 % within 90 days of admission, while 38.5 % were readmitted within 90 days of discharge (39). These findings highlight the ongoing vulnerability of this population and the importance of effective post-exacerbation care and follow-up (17).

Although population-level mortality rates have gradually declined over the past decade, COPD continues to represent a major cause of premature death and health inequality in England. These findings underscore the need for continued efforts to prevent exacerbations, optimise inpatient and discharge management, and address regional and deprivation-related disparities in COPD outcomes.

1.4.3 Disease burden

1.4.3.1 Clinical burden

1.4.3.1.1 Symptoms

COPD is associated with persistent respiratory symptoms including dyspnoea (breathlessness), cough with phlegm, frequent chest infections and persistent wheezing (82). Symptom burden worsens with disease severity and declining lung function (83), with disease progression leading to significant impairments in daily functioning, wellbeing and overall health status, with a loss of independence and increased risk of anxiety and depression (84, 85).

A Spanish cross-sectional study (N=2,669; 2015 (86)) highlighted that patients at high-risk of exacerbations (GOLD Group C and D, now Group E, defined as ≥ 2 exacerbations per year, or ≥ 1 requiring hospitalisation) experience more severe symptoms, greater impact on health-related quality of life (HRQoL), and more disruption to daily life and sleep quality. Importantly, a higher symptom burden is also associated with an increased exacerbation risk. In the UK CPRD cohort (N=40,425; April 2009–March 2011 (87)), patients with moderate to severe dyspnoea (Medical Research Council [MRC] ≥ 3) had a 46% higher risk of exacerbations, while patients with mild dyspnoea (MRC ≥ 2) had an 18% higher risk, compared with those with no dyspnoea.

The burden of disease for those with eosinophilic COPD is particularly substantial, as frequent exacerbations contribute to lung function decline, causing progressive breathlessness, reduced exercise capacity, and increased dependence on healthcare services (88, 89).

1.4.3.1.2 Comorbidities

Systemic inflammation in COPD contributes to a high burden of comorbid conditions, increasing the likelihood of cardiovascular (CV), neurological, gastrointestinal, metabolic and

non-COPD respiratory diseases (10). Key COPD-related complications include depression, anxiety, cor pulmonale, chest infections, respiratory failure, pneumothorax, polycythaemia, cachexia, and lung cancer (90).

A UK primary care study (N=1.27 million) reported that 86% of patients with COPD had ≥ 1 comorbidity, compared with 48.9% in patients without COPD. A significantly higher proportion of patients with COPD (over 22%) had ≥ 5 comorbidities vs. those without (4.9%) (adjusted odds ratio [OR]: 2.63) (91). Similar patterns were reported in a Scottish primary care cohort, where 82% of people with COPD had ≥ 1 additional long-term condition, and nearly half (46%) had ≥ 3 , making COPD one of the conditions most strongly associated with multimorbidity and polypharmacy in primary care (92). In the REPOSI study of hospitalised older adults in Italy, 67% of patients were prescribed five or more medications at discharge (93). The highest mean number of drugs (≥ 8) was seen in clusters involving heart failure (HF) and COPD, HF and chronic renal failure (CRF), and COPD and coronary heart disease (CHD), where patients typically received eight to nine medications (93). Analyses using the UK Biobank further confirm the high prevalence of multimorbidity and polypharmacy in COPD (94). Among more than 8,000 participants with self-reported COPD, 17% had four or more comorbidities compared with 4% without COPD, and 52% were taking five or more medications compared with 18% without COPD (94). Polypharmacy is linked to adverse drug reaction risk, and patients with COPD are significantly more likely to be prescribed multiple medications associated with falls, bleeding, renal injury, or central nervous system depression (94, 95).

Comorbidities in patients with COPD are associated with increased risk of mortality (96). A UK analysis of 107,761 hospitalised COPD exacerbation cases (2018–2020) demonstrated that patients with a higher comorbidity burden (Charlson index) had a significantly increased risk of 30- and 90-day mortality (97). Moreover, comorbidities exacerbate disease severity, increase healthcare use, and negatively impact patient QoL and survival (96, 98). UK data consistently show that COPD is associated with a high burden of multimorbidity and polypharmacy, and that comorbidity burden contributes to more frequent exacerbations and poorer outcomes (92, 96). Shared systemic inflammation between COPD and common comorbidities such as CV disease, diabetes, and depression, along with reduced physiological reserve and the complexity of managing multiple medications, can heighten vulnerability to exacerbations and complicate recovery (96, 98-100).

1.4.3.1.3 Exacerbations

COPD exacerbations typically present as acute episodes of worsened respiratory symptoms beyond normal daily symptom variation, and can result in additional need for therapy, treatment in an outpatient clinic or emergency department (ED), or may require hospital

admission, depending on the severity (10). They accelerate the deterioration of lung function and as the severity of airflow limitation increases, exacerbations can become more frequent and more severe. Evidence also suggests that the effects of moderate and severe exacerbations extend beyond the acute event itself, contributing to lasting loss of lung function and overall disease progression. In a post-hoc analysis of the four-year UPLIFT study, conducted across 37 countries, the annual rate of decline in post-bronchodilator FEV₁ nearly doubled after a single exacerbation compared with the pre-event rate, indicating a sustained worsening rather than a transient change (12). Persistent airway and systemic inflammation following exacerbations may drive these longer-term effects (12, 101, 102), and individuals with less severe obstruction may experience greater absolute losses owing to their higher baseline lung function (103, 104).

Hospitalisation and mortality

COPD exacerbations can increase the likelihood of hospitalisation, the risk of mortality, CV events, and contributes to disease progression whilst also increasing the risk of future exacerbations. As COPD progresses, exacerbations become more frequent and are associated with worsening health status, accelerated decline in lung function, and cumulative physiological injury over time (54, 82, 105). Recurrent exacerbations result in worsening of symptoms and QoL, with an increase in hospitalisations and ED visits (11, 16). A US retrospective cohort study with patients newly diagnosed with COPD found the risk of death and CV events was greatest in the first 30 days and rose with subsequent exacerbations (16). Risks were increased for 1–2 years following moderate and severe exacerbations; each subsequent acute exacerbation was associated with incrementally higher rates of both death and CV events, indicating sustained increased cardiopulmonary risk.

Severe exacerbations are a leading cause of morbidity and mortality for patients with COPD and their occurrence often signals a rapid deterioration in health status (15). A Hungarian retrospective analysis reported that a severe exacerbation increases the risk of another exacerbation by 64% and increases the risk of death by 21% (47). In a population-based Canadian cohort, each hospitalised exacerbation markedly increased the risk of subsequent events and death, with mortality peaking during the first week after admission before dropping over 3 months (15). Similarly, a Spanish cohort study of patients hospitalised due to acute exacerbations, reported a hospital-mortality rate of 4.8% among these patients, with a 1-year mortality rate of 26%, and a 5-year mortality rate of 64% (14).

Recent national audit data report that 7.5% of patients hospitalised for a COPD exacerbation die within 30 days of admission, 14.2% within 90 days, and 38.5% are readmitted within 90

days of discharge (39). Similar outcomes were observed in an earlier European COPD Audit, with 4.3% in-hospital mortality and 15% 90-day mortality (38).

Elevated blood eosinophil levels

Up to 40% of patients with COPD have T2 inflammation (identified by elevated blood eosinophil levels) as an underlying pathology (3-7). T2 inflammation contributes to a self-perpetuating cycle of exacerbations (12, 106). Studies suggest that patients with elevated blood eosinophil levels have a 30% higher risk of exacerbations vs. those without elevated levels:

- Data from COPDGene, and ECLIPSE cohorts demonstrated $\text{BEC} \geq 300$ cells/ μL was predictive of higher exacerbation risk, and that the risk was greater in patients with ≥ 2 prior exacerbations, with an incidence rate ratio (IRR) of up to 1.96 (8).
- A US cohort study (N=7,245) reported that $\text{BEC} \geq 300$ cells/ μL was associated with a 25% increased exacerbation risk within 12 months (adjusted relative risk: 1.25) (107).
- A European (Copenhagen) study (N=7,225) linked $\text{BEC} \geq 340$ cells/ μL to higher risk of both moderate and severe exacerbations (IRR 1.15 and 1.76, respectively). Risk increased further in patients with prior exacerbations (IRR up to 3.21) (108).

The prevention of exacerbations is therefore key in the long-term management of COPD, as supported by the 2025 GOLD report (10).

1.4.3.2 Quality of life burden

1.4.3.2.1 Symptoms

COPD symptoms, including dyspnoea (breathlessness), cough with phlegm, frequent chest infections, and persistent wheezing, negatively impact patients' daily activities, functioning, and wellbeing (82), which often contribute to a "spiral of decline" as health deteriorates over time (109). Sleep disruption caused by dyspnoea (breathlessness) and cough with phlegm further reduces HRQoL and contributes to anxiety and fatigue (82).

In a multinational survey, patients most frequently reported cough (42%), dyspnoea (37%), fatigue (37%), and sputum production (35%) as symptoms affecting wellbeing (110). A study in European patients with COPD reported that greater dyspnoea (mMRC ≥ 2) is associated with lower HRQoL (111). Many of these patients continue to experience dyspnoea despite treatment and at levels associated with notable impairments in the patients' ability to function across a multitude of domains (111).

1.4.3.2.2 Exacerbations

Patients who experience an exacerbation have reduced QoL vs. those who do not (36). A meta-analysis showed that moderate and severe exacerbations have a significant and cumulative impact on HRQoL; each moderate and severe exacerbation worsened SGRQ scores by +1.88 and +2.92 points, respectively, and EQ-5D utility scores declined by -0.02 and -0.03 per event, respectively (13).

Exacerbations frequently lead to functional loss, with 45% of patients becoming bed- or couch-bound and 55% stopped work after community-treated exacerbations (112). A multinational study reported that 86% of patients had significant activity limitations, and 47% stopped all activity during exacerbations (113). Recovery is often prolonged and QoL seldom returns to pre-exacerbation levels (36). Approximately 20% of patients with moderate-to-severe exacerbations do not return to baseline by 8 weeks (10, 37).

Exacerbations are a leading cause of morbidity and mortality for patients with COPD due to the short-term impacts on lung function and QoL and long-term impacts on disease progression (10, 12, 38, 81). In a UK cohort study (N=101), median symptom recovery was 7 days, with 14% lasting beyond 5 weeks and 9% over 13 weeks (37). The GLOBE study found a 9.6-point difference in SGRQ score at 26 weeks between patients with recurrent exacerbations and those without, indicating limited recovery with repeat events (36). A systematic review suggested that patients view exacerbations as the most important clinical outcome due to their severe impact on independence and QoL (114).

1.4.3.2.3 Anxiety and depression

Anxiety and depression are more common in patients with COPD than in the general population or patients with other chronic diseases (115-120). The prevalence of depression ranges from 10–42% in patients with stable COPD, and up to 86% in hospitalised patients (117, 121). A UK cohort study showed that the risk of depression increased with disease severity (OR: 2.01 in severe COPD) (122).

Anxiety is also highly prevalent and occurs in 13–46% of outpatients and 10–55% of inpatients (123), and the prevalence of panic disorders may be up to 10-fold more common than in the general population (115, 124). Depression and anxiety frequently co-occur and are reported in 26–43% of patients with COPD, and are associated with greater physical disability, suicidal ideation, and persistent symptoms (125-127). Studies demonstrated that depression and anxiety worsen COPD outcomes through increased mortality (128, 129), symptom burden (130), exacerbation risk (131), HCRU (129, 132, 133), and decreased HRQoL and social functioning (120, 134, 135).

1.4.3.2.4 Physical limitations

A 2017 US cross-sectional survey (N=1,775) found that patients in GOLD C/D (now GOLD E) had the greatest physical limitations (mean Functional Performance Inventory-Short Form [FPI-SF] score: 1.9), compared with 2.6 in GOLD A and 2.1 in GOLD B (136). This contributes to caregiver burden and further HRQoL decline.

1.4.3.2.5 Impact on caregivers

Caregivers of people with COPD experience significant emotional, physical, social, and financial burden, often reporting depression, anxiety, fatigue, social isolation, and lack of preparedness to manage symptoms or exacerbations (137). Informal caregivers (e.g. spouses, adult children) play a key role in daily care, medication management, symptom monitoring, and responding to exacerbations, often without formal training or external support.

A 2025 mixed methods study found that COPD exacerbations place significant emotional, physical, and logistical stress on caregivers, who report feeling unprepared, socially isolated, and overwhelmed by emergency decision-making responsibilities. Caregivers highlighted exacerbations as the most distressing aspect of the condition and expressed a strong need for better support and communication from healthcare providers (138).

In a UK COPD patient voices report, caregivers highlighted the personal costs of their caring role, which has a significantly impact on their own relationships, work, finances, and personal time (43). Around 50% of caregivers undertake caring ≥ 50 hours a week, and the majority were over the age of 65 and coping with their own long-term conditions, such as diabetes and heart disease, with reduced ability to focus on their own needs (43).

The impact on caregivers is an under-recognised component of COPD burden and should be considered in evaluating interventions that reduce exacerbation frequency or severity. As individuals with COPD often rely heavily on caregivers for daily support, there is a growing preference for home-based care services (138). Studies have shown home-based programmes have improved caregiver burden, anxiety, depressive symptoms, and fatigue (139, 140).

1.4.3.3 Economic burden

1.4.3.3.1 Overall burden

COPD is associated with high direct and indirect costs, largely driven by exacerbations, disease severity, high resource use and caregiver support needs (Sections 1.4.3.3.2–1.4.3.3.4).

In the UK, annual National Health Service (NHS) spend on COPD is estimated at £2 billion (18). Patients with moderate-to-severe COPD in the primary care setting often require frequent general practitioner (GP) and specialist visits, reflecting high resource use (141). Real-world retrospective UK cohort studies have shown that patients with COPD incur substantial healthcare costs, with total, medication, and hospitalisation-related expenditures increasing with disease severity and exacerbation frequency (142-144). In newly diagnosed and established COPD populations, annual management costs ranged from £1,523 in patients with no exacerbations to £3,396 in those with two or more exacerbations per year, increasing with worsening dyspnoea and greater airflow limitation (142, 143). More recent data also indicate that optimising therapy, such as switching from multiple-inhaler to single-inhaler triple therapy, can reduce exacerbation rates, healthcare resource use, and associated direct medical costs in UK primary care (144).

In fact, COPD exacerbations are the leading contributor to the overall economic burden of COPD (10). The estimated costs of managing moderate and severe exacerbations in England is predicted to rise from £0.6 billion in 2011 to over £1 billion by 2030 (40).

1.4.3.3.2 Direct healthcare costs and healthcare resource use

A UK CHOPIN model study projected that cumulative COPD healthcare costs will exceed £46 billion between 2021 and 2040 (18). The cost burden by COPD severity was:

- Mild: £10.3 billion
- Moderate: £20.8 billion
- Severe: £7.8 billion
- Very severe: £5.3 billion.

The total costs are driven by both routine management (55%) and exacerbations (45%) (18). Exacerbations therefore represent a key target for cost reduction within COPD management in Europe, given their substantial contribution to overall healthcare expenditure (48). These cumulative projections from the CHOPIN model are supported by other analyses showing a similar upward trend in annual COPD-related healthcare expenditure. Specifically, McLean *et al.*, 2016 estimated that annual direct healthcare costs of COPD in England will rise from £1.5 billion in 2011 to £2.32 billion by 2030, with the costs of managing moderate and severe exacerbations increasing from £0.6 billion to over £1 billion during the same period (40).

A retrospective UK study (N=7,881) reported annual COPD management costs of £2,047/patient, increasing with severity (143) with patients with mild, moderate, severe or very severe airflow obstruction incurring costs of £1,921, £2,046, £2,092 and £2,293 per patient per year, respectively. Another retrospective study using CPRD-HES data in England

(N=44,201), found that General Practitioner (GP) visits ranged from 4.72 (95% CI 4.62–4.84) (GOLD A) to 6.91 (95% CI 6.75–7.10) (GOLD D) per person-year, while COPD-related hospitalisations rose from 0.35 (95% CI 0.31–0.40) to 0.85 per person-year, and non-COPD hospitalisations ranged from 0.28 (95% CI 0.27–0.30) (GOLD D) to 0.42 (95% CI 0.41–0.44) (GOLD B) per person-year (145).

COPD accounts for 1.4 million GP consultations annually (146). It is also the second leading cause of emergency admissions in the UK (approximately 130,000/year), leading to 108,891 admissions in England alone in 2022/23 (147). Readmission remains high, with 24.4% of patients readmitted within 30 days of discharge from hospital and 43.1% within 90 days (97). Seasonal surges in exacerbations (e.g. winter) may create opportunity costs and strain NHS capacity (148).

A cross-sectional study reported that the mean length of stay for hospitalised COPD exacerbations across 13 European countries was 8.7 days (149). In the OLIN study (Sweden), severe exacerbations were on average 10 times more costly than moderate exacerbations; with hospitalisation account for 67% of exacerbation-related costs (48).

International data suggest higher economic and healthcare burden in COPD patients with T2 inflammation. This includes increased hospitalisations, where for example, a Canadian retrospective study (N=167) (150), found that COPD patients hospitalised with elevated eosinophils (≥ 200 cells/ μ L or $\geq 2\%$) had a 3.6 times higher risk of 12-month COPD-related readmission; a 2.3 times higher risk of all-cause readmission; and shorter time to first COPD-related readmission (hazard ratio [HR]: 2.78). In addition, patients with elevated blood eosinophils who experience exacerbations account for up to 52% higher medical costs compared with those with lower BEC. A US retrospective study (2017–2023) reported that COPD patients with T2 inflammation (BEC ≥ 300 cells/ μ L) and frequent exacerbations had higher rates of moderate/severe exacerbations and increased COPD-related HCRU and costs over 12 months compared with a reference group without these characteristics (n=1,631 vs. n=11,203) (151).

1.4.3.3 Indirect costs and productivity losses

COPD causes significant indirect costs due to work limitation and absenteeism, early retirement, and premature mortality. Many patients with COPD are of working age, and the disease often affects individuals during their most productive years (10); therefore, the indirect costs associated with COPD are also considerable.

The Continuing to Confront COPD International Patient Survey conducted in the UK found that of 305 patients, 52% of patients were completely unable to work, while 18% had a reduced ability to work (152). According to the cost of illness model developed by Asthma and Lung

UK (99), the total productivity costs of COPD in England were estimated to be £1.7 billion in 2023. The total costs associated with quality-adjusted life years (QALY) losses due to moderate/severe exacerbations and adverse events (AE) of COPD were estimated to be £2.3 million.

1.4.3.3.4 Caregiver costs

In a UK COPD patient voices report, financial issues were raised by caregivers with the cost-of-living crisis having a profound impact on them. Falling into debt or cutting back on activities to improve their own health and wellbeing were highlighted (43).

A Spanish caregiver study (N=220,892) found that among caregivers under the age of 65, 37.3% had work-related impacts, 22.7% could not work outside the home, and 11.5% stopped working altogether (140).

1.4.4 Clinical pathway of care

There are currently no definitive pathways in place for COPD patients to receive biologic treatments in the UK. Several recent frameworks emphasise the importance of a clear, integrated clinical pathway for COPD care. These aim to reduce unwarranted variation, improve patient experience, and ensure that people with COPD receive timely and equitable support across the system:

- The four fundamental pillars of COPD care are (43): diagnosis, information, monitoring, and treatment. These provide the structural basis for a comprehensive pathway, ensuring early and accurate diagnosis, access to self-management support, proactive monitoring, and both pharmacological and non-pharmacological treatments (NICE's five fundamentals: self-management, smoking cessation, pulmonary rehabilitation, vaccinations, and comorbidity management [Section 1.4.4.1.1]).
- A networked delivery model (43), emphasising that care should be organised by type and complexity rather than location, with equitable access across Integrated Care Systems (ICS). In practice, this means most people with COPD are managed in primary care (diagnosis, inhaled therapies, rescue packs, and self-management support), with community respiratory teams providing pulmonary rehabilitation, education, and home-based support. Secondary care manages more complex cases through outpatient clinics and inpatient treatment of exacerbations, while acute settings provide urgent care and opportunities to optimise long-term therapy.
- Integrated COPD service framework (43), enabling Integrated Care Boards (ICB) to align resources, commission consistently, and embed multidisciplinary pathways that join up hospital, community and primary care.

- Population-based and data-driven approaches (43), to ensure care is tailored to local need, reduce variation, and target interventions at vulnerable groups (e.g. deprived or rural populations).

Together, these frameworks outline a shift towards joined-up, multidisciplinary COPD pathways that are proactive rather than reactive, and that address health inequalities by ensuring consistent access to diagnostics, pulmonary rehabilitation, biologics, and psychosocial support. They also promote a personalised and holistic approach to COPD management, including patient preferences, with a major goal of better community management and preventing hospital readmissions (153, 154).

1.4.4.1 Current treatment for COPD in England

The management of COPD in England is guided by NICE guideline NG115 (last updated in 2019) (19), which outlines a stepwise, personalised approach to treatment based on symptom severity, exacerbation history, and the presence of asthmatic features or eosinophilic inflammation.

The GOLD 2025 report framework (10) is also widely used in clinical practice to support patient stratification, offering a practical clinical framework for treatment based on symptoms and exacerbation risk, and informs the design of most clinical trials.

1.4.4.1.1 Non-pharmacological interventions (NICE “fundamentals of COPD care”)

NICE recommends all patients receive five core non-pharmacological interventions, known as the “fundamentals of care” prior to and in conjunction with pharmacological treatment. These are:

- Smoking cessation support
- Annual influenza and pneumococcal vaccinations
- Pulmonary rehabilitation (if indicated)
- Personalised self-management plans
- Management of comorbidities.

Despite their central role, uptake of these interventions is low and their use is inconsistent across England. The most recently published survey from Asthma and Lung UK indicates that care for COPD patients has not returned to pre-pandemic levels, and only 17.6% of individuals had received all five fundamentals (155).

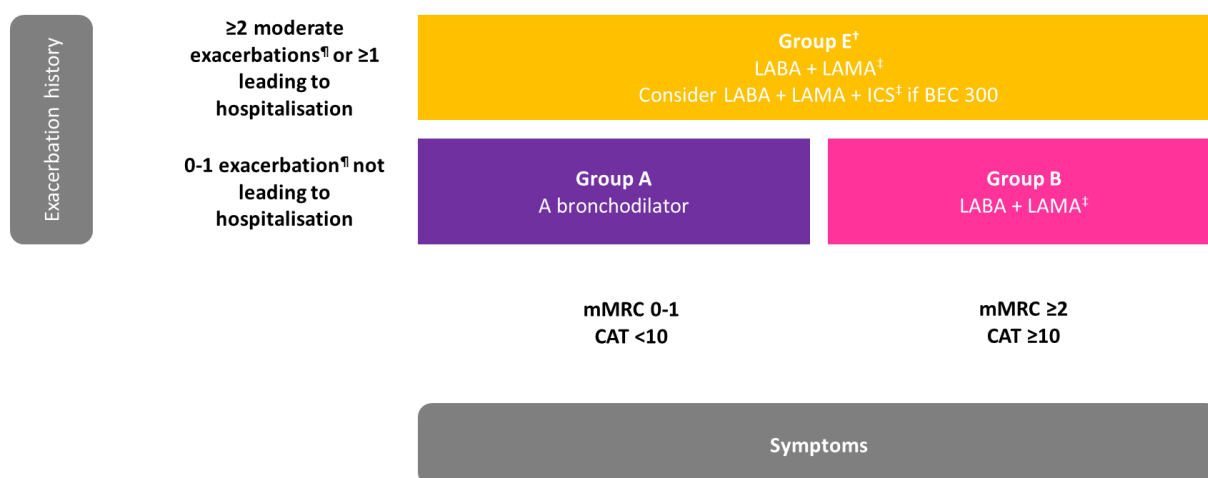
1.4.4.1.2 Pharmacological treatment

NICE also recommends that following initiation of non-pharmacological care, inhaled pharmacological treatment is introduced and escalated based upon ongoing symptoms and exacerbation history (19):

- Patients begin with short-acting bronchodilators (short-acting beta₂-agonist [SABA] or short-acting muscarinic antagonist [SAMA]) for symptom relief.
- If symptoms or exacerbations persist, treatment is escalated. For patients without asthmatic features, the next step is dual long-acting bronchodilation with a LAMA plus a LABA. Where asthmatic features or evidence of steroid responsiveness are present – such as a history of asthma, atopy, or a higher blood eosinophil count – a LABA combined with an ICS is considered appropriate.
- If symptoms remain uncontrolled, triple therapy with LAMA, LABA, and ICS may be introduced. This escalation is particularly recommended in people who continue to have troublesome symptoms or exacerbations on dual therapy, or in those with a history of ≥ 2 moderate or one severe exacerbation(s) in the previous year. A trial of triple therapy can also be considered in patients with poor quality of life, but treatment should be stopped if no benefit is seen after three months. As ICS use carries an increased risk of pneumonia, it should only be continued where a clear clinical benefit is demonstrated.

This approach reflects standard clinical practice in England, where treatment is adjusted based on dyspnoea scores, CAT results, and exacerbation history, with escalation based on clinical response (19), and is aligned with GOLD's stepwise escalation (Figure 3) (10).

Figure 3: GOLD 2025 stepwise pharmacological treatment of COPD



Source: GOLD 2025 (10).

[†]In the presence of concomitant asthma, patients with COPD should be treated like patients with asthma. In this circumstance, the use of ICS is required; [‡]Single inhaler therapy may be more effective than multiple inhalers in

improving adherence to treatment; ¶Exacerbations refers to the number of exacerbations per year
Abbreviations: BEC, blood eosinophil count; CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA, long-acting beta₂-agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Research Council.

1.4.4.1.3 Adjunct and supportive pharmacological therapies

Several additional pharmacological treatments may be considered for symptom relief or specific clinical phenotypes (19, 156):

- Theophylline may be offered in select cases where inhaled therapies are not effective or suitable, though use is limited due to the need for monitoring and a narrow therapeutic index
- Mucolytics are considered for patients with a chronic productive cough to aid sputum clearance, particularly in those with features of chronic bronchitis (CB)
- Oral corticosteroids and antibiotics are reserved for acute exacerbation management and are not recommended for long-term use due to safety concerns.

1.4.4.1.4 Add-on therapies beyond triple therapy

For patients who continue to experience exacerbations despite optimised triple inhaled therapy, options are limited:

- Roflumilast (NICE TA461) (45) is recommended for adults with severe COPD (FEV₁ <50%), chronic bronchitis, and ≥2 exacerbations/year. However, its use in practice is rare due to high discontinuation rates (up to 70%) and AEs, particularly gastrointestinal and psychiatric symptoms. Real-world data suggest only ~5% of eligible patients in England are prescribed roflumilast (46)
- Azithromycin (19), a macrolide antibiotic, is recommended off-label for non-smokers with ≥4 exacerbations/year and chronic sputum production. Its use is limited to a small subgroup with non-eosinophilic inflammation and is associated with risks including QT prolongation, hearing loss, and increased antimicrobial resistance (AMR). It is not relevant for patients with T2 inflammation and lacks supportive evidence when added to triple therapy.

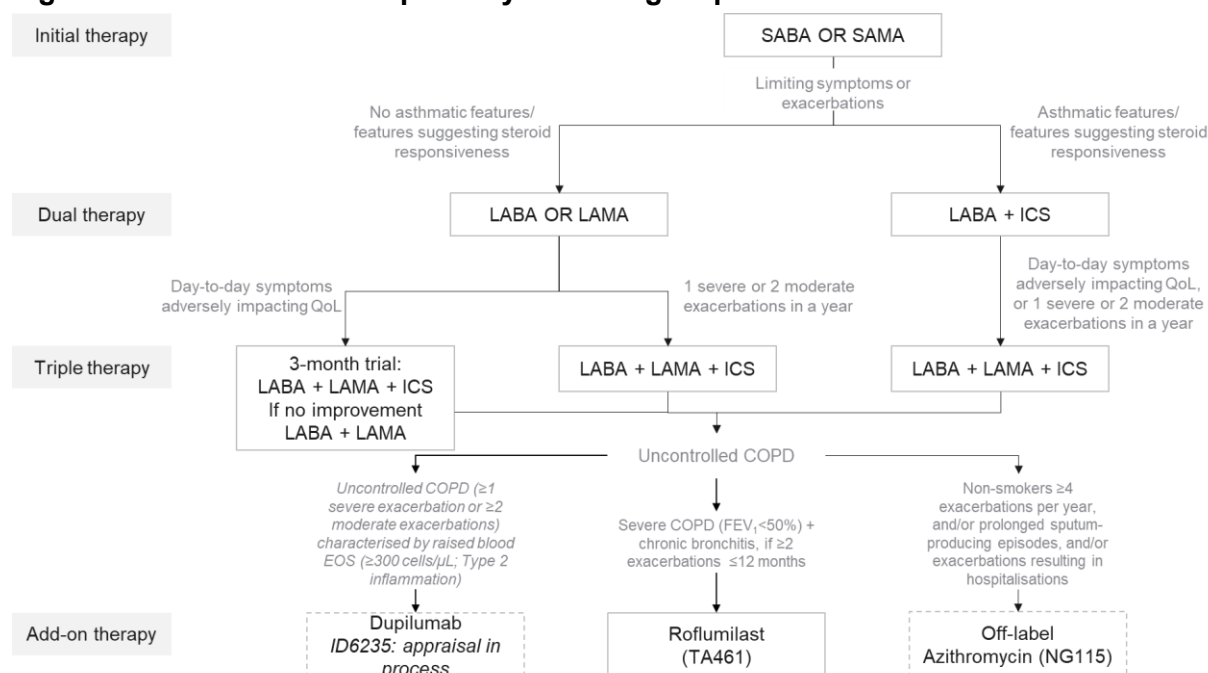
There are currently no therapies routinely available within the NHS specifically for patients with COPD and T2 inflammation who continue to experience exacerbations despite triple therapy, representing a significant unmet need.

NICE is currently appraising dupilumab (an IL-4/IL-13 inhibitor) as an add-on maintenance treatment for uncontrolled COPD in adults with raised blood eosinophils, who are receiving an ICS, a LABA, and a LAMA (triple therapy), or a LABA, and a LAMA (double therapy) if ICS are

not appropriate (20). Final guidance is imminent, which, if positive, would make dupilumab the first biologic treatment available within the NHS for this subgroup (20).

The current UK clinical pathway of care based on NICE technology appraisal guidance is summarised in Figure 4.

Figure 4: Current treatment pathway excluding mepolizumab



Source: NICE NG115 (19); NICE TA461 (45); NICE ID6235 GID-TA11246 (20).

Abbreviations: COPD, chronic obstructive pulmonary disease; EOS, eosinophils; FEV₁, forced expiratory volume in 1 second; ICS, Inhaled corticosteroids; LABA, long-acting beta₂-agonist; LAMA, long-acting muscarinic antagonist; NG, NICE Guideline; QoL, Quality of life; SABA, short-acting beta₂-agonist; SAMA, short-acting muscarinic antagonist TA, technology appraisal.

1.4.5 Unmet need

Despite current treatment pathways and the widespread use of inhaled therapies, a substantial proportion of patients with COPD continue to experience frequent exacerbations and poor outcomes. Up to 40% of patients have evidence of T2 inflammation (3-7), commonly identified by BEC ≥300 cells/μL (8), and are at higher risk of exacerbations (8, 107). This subgroup experiences substantial clinical (Section 1.4.3.1), humanistic (Section 1.4.3.2) and economic burden (Section 1.4.3.3).

Currently, treatment options are limited for patients who continue to exacerbate despite triple inhaled therapy, and there are no targeted biologic therapies routinely available within the NHS. Dupilumab (an IL-4/IL-13 inhibitor) is currently under NICE appraisal (ACM2, 5 August 2025) as an add-on maintenance treatment for uncontrolled COPD in adults with raised blood eosinophils, with final guidance imminent (20). Roflumilast is rarely used due to numerous AEs and high discontinuation rates (46), and azithromycin is limited to a small subgroup of

patients with non-eosinophilic inflammation and therefore not relevant for those with T2 inflammation (19). In addition, it is associated with risks of severe AEs and high rates of AMR.

IL-5 is a fundamental inflammatory mediator in patients with COPD driven by T2 inflammation, both in stable states and during exacerbations (56, 66, 68-71), and at present, there are no NHS commissioned biologic therapies targeting IL-5 or the underlying T2 inflammatory pathway. Following an anticipated positive NICE recommendation for dupilumab, NHS-commissioned biologic therapies would be expected to extend to agents targeting IL-5 and the underlying T2 inflammatory pathway.

Given the elevated risk of exacerbations, mortality, and healthcare use in this population, alongside the absence of targeted therapies beyond inhaled steroids, there is a strong rationale for introducing new, mechanism-based treatments aimed specifically at patients with T2 inflammation who remain symptomatic despite SoC.

1.4.6 Positioning of mepolizumab

Mepolizumab is anticipated to be used as an add-on maintenance treatment for adult patients with uncontrolled COPD (defined as ≥ 2 moderate or ≥ 1 severe exacerbations within 12 months) of an eosinophilic phenotype (defined as ≥ 300 cells/ μ L) on a combination of an ICS, a LABA, and a LAMA. Dupilumab (an IL-4/IL-13 inhibitor) is currently undergoing NICE appraisal as an add-on maintenance treatment for uncontrolled COPD in adults with raised blood eosinophils, with final guidance imminent (20). Mepolizumab represents a similar, yet mechanistically distinct, biologic, directly targeting the IL-5 pathway rather than IL-4/IL-13 signalling, for reducing exacerbations in this target population.

Mepolizumab (Nucala®) is a humanised immunoglobulin G, subclass 1, κ light chain (IgG1 κ) monoclonal antibody that specifically binds to IL-5, a central cytokine in T2 inflammation (52). IL-5 is the key driver of eosinophil development, activation, recruitment, and survival processes implicated in exacerbations and airway inflammation in COPD. By neutralising IL-5, mepolizumab reduces eosinophil levels and activity, thereby interrupting the inflammatory cascade that contributes to mucus plugging, barrier dysfunction, airway remodelling, and alveolar destruction (52).

IL-5-driven inflammation has also been linked to non-eosinophil cell types, including epithelial cells, fibroblasts, neutrophils, and smooth muscle, though the mechanisms in COPD remain under investigation. Elevated IL-5 has been detected in serum and sputum of patients with moderate-to-severe COPD and is associated with worse clinical outcomes (75).

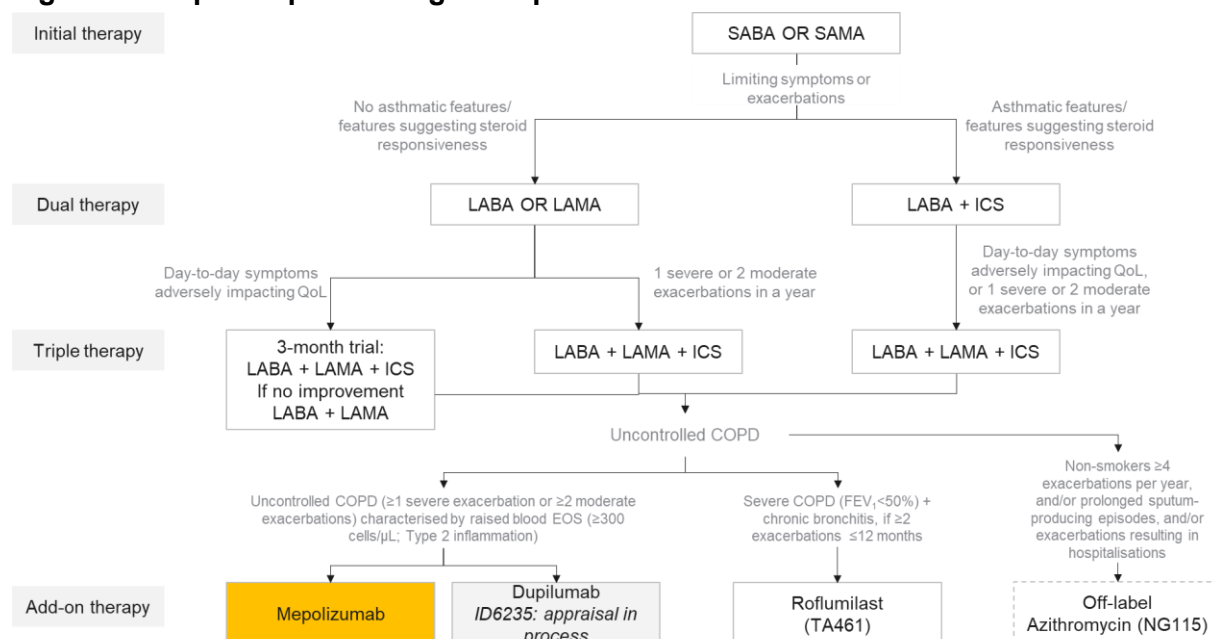
Mepolizumab is the first biologic to target IL-5 in COPD. The clinical development programme for mepolizumab in COPD was initiated to evaluate whether targeted inhibition of IL-5 could

reduce exacerbation rates in patients with T2 inflammation who continue to exacerbate despite receiving optimised inhaled therapy. While dupilumab blocks IL-4 and IL-13 signalling to reduce T2 inflammation, mepolizumab directly targets the eosinophil pathway, with both biologics aimed at reducing exacerbations in patients with eosinophilic COPD. Mepolizumab has been studied across a broad spectrum of patients with eosinophilic COPD across the different GOLD categories, as well as in various subgroups, including patients with CB, emphysema, and mixed phenotypes (21, 22, 24, 25, 34). The development programme includes the pivotal MATINEE trial (21, 22), building on findings from METREX (24) and METREO (25, 34) (Appendix J).

Mepolizumab is administered subcutaneous (SC) injection every four weeks (Q4W), compared with every 2 weeks (Q2W) for dupilumab (28, 157). Less frequent dosing may reduce treatment burden and align better with patient preference, which in turn can support adherence and persistence with therapy (31). Improved adherence is particularly important in COPD, where comorbidities and polypharmacy already contribute to high treatment burden (32). Another study investigating patient-determined attributes of COPD treatment (including UK, US, and German patients) found that lower frequency of use was among the favoured attributes for current treatment, and that most participants would consider a switch in medication, mainly for improved efficacy, but also to reduce medication frequency (30). Mepolizumab has a well-established safety profile and 10+ years of clinical use across eosinophilic diseases (52). It has been studied in over 3,000 patients across 26 clinical trials and is approved for use in four eosinophilic conditions globally, including severe asthma, chronic rhinosinusitis with nasal polyps (CRSwNP), eosinophilic granulomatosis with polyangiitis (EGPA), and hypereosinophilic syndrome. Real-world evidence in asthma (including some patients with co-morbid COPD) reinforces mepolizumab's efficacy and tolerability (158).

The proposed positioning of mepolizumab is provided in Figure 5.

Figure 5: Proposed positioning of mepolizumab



Source: NICE NG115 (19); NICE TA461 (45); NICE ID6235 GID-TA11246 (20).

Abbreviations: COPD, chronic obstructive pulmonary disease; EOS, eosinophils; FEV₁, forced expiratory volume in 1 second; ICS, Inhaled corticosteroids; LABA, long-acting beta₂-agonist; LAMA, long-acting muscarinic antagonist; NG, NICE Guideline; NICE, National Institute for Health and Care Excellence; QoL, Quality of life; SABA, short-acting beta₂-agonist; SAMA, short-acting muscarinic antagonist TA, technology appraisal.

1.5 Equality considerations

COPD disproportionately affects people in deprived areas, where risk factors such as smoking, air pollution, and poor housing conditions are more prevalent (159). Individuals from socioeconomically disadvantaged backgrounds with multiple comorbidities are disproportionately impacted by COPD and are consequently at higher risk of experiencing exacerbations and hospitalisations than the general population (49, 50). A survey from Asthma and Lung UK indicated that the most deprived 10% of households are more than 2.5 times more likely to have COPD than the most affluent 10% of households (155). Those living in the most deprived 10% of households are more than 2.5 times more likely to have COPD than the most affluent 10% (155). People with fewer resources also tend to have more frequent exacerbations and reduced access to consistent, high-quality care (49, 160), leaving them increasingly disadvantaged in the management and outcomes of their disease.

Access to specialist diagnosis and care is currently inequitable. Geographical disparities are evident, with higher COPD rates in Northern England and rural regions compared with London and the South (159). Many patients in these areas face significant barriers to accessing specialist care services, often needing to travel long distances for treatment (159). Patients also highlighted differences in the quality and availability of the COPD services they needed

depending on where they live and the healthcare providers they access, which is compounded by health inequalities such as deprivation, rurality and ethnicity (43).

Vital services for support, such as pulmonary rehabilitation (an exercise and education programme to help with breathlessness management (161)) is an important tool in improving the QoL for patients with COPD. However, it is not offered early enough or is not accessible, particularly for those whom English is not a first language. According to a UK COPD patient voices report, many patients found difficulty accessing pulmonary rehabilitation, with very long waits (43). In some areas, it is only accessible once a year, whereas other areas have no availability at all.

Digital exclusion remains a major challenge in equitable COPD care, as limited access to and confidence with technology can restrict the use of digital health tools such as remote monitoring, telehealth, and online self-management programmes. Evidence shows that older adults, people in deprived or rural areas, and those with lower digital literacy are less likely to engage with these interventions, which risks widening existing health inequalities between affluent and disadvantaged groups (162, 163). While digital platforms can enhance COPD self-management, adherence, and early detection of exacerbations, their benefits are not evenly distributed, highlighting the need for inclusive, user-centred design, affordable connectivity, and targeted support to build digital confidence (162-164). As the King's Fund notes, digital transformation should promote inclusion, through co-design, digital literacy initiatives, and community-based access, to ensure that innovations in COPD care reduce, rather than reinforce, health disparities (165).

In addition, some patients may face barriers to attending healthcare appointments, including psychosocial and practical challenges (51). The potential to reducing these through less frequent dosing acknowledges and accommodates patterns of healthcare avoidance.

The impact of a well-tolerated and effective treatment in reducing exacerbations on these patients and on reducing inequalities, that may also help to reduce healthcare encounters, should be considered.

2 Clinical effectiveness

Key messages

- The clinical trial programme for mepolizumab investigated a wide spectrum of patients with COPD with T2 inflammation characterised by raised BEC. The trial populations included patients with a wide spectrum of airflow obstructions, the full range (0–4) of modified Medical Research Council (mMRC) dyspnoea scale grades, and patients regardless of symptoms of chronic bronchitis (CB) or COPD phenotype (21-26).
- The annualised rate of moderate and severe exacerbations, used as the primary endpoint in key trials, captures the key driver of disease progression and outcomes, making it a clinically meaningful measure of treatment impact.
- **MATINEE** was a pivotal global Phase 3, placebo-controlled, double-blind, randomised, multicentre trial evaluating subcutaneous (SC) mepolizumab vs. placebo as add-on to maximal inhaled triple therapy (LABA + LAMA + ICS) (21, 22).
 - Mepolizumab significantly reduced the annualised rate of moderate/severe exacerbations by 21% (rate ratio [RR] 0.79 [95% confidence interval (CI): 0.66, 0.94]; $p=0.011$) vs. placebo, with data up to 2 years (21, 22).
 - The time-to-first moderate or severe exacerbation was longer with mepolizumab than with placebo (median 419 vs. 321 days; hazard ratio [HR]: 0.77 [95% CI: 0.64, 0.93]; $p=0.009$), sustained for up to 2 years (21, 22).
 - Mepolizumab nominally significantly reduced the annualised rate of exacerbations leading to emergency department (ED) visits and/or hospitalisations by 35% vs. placebo, with data up to two years (RR: 0.65 [95% CI: 0.43, 0.96]) (21, 22).
 - Mepolizumab numerically improved QoL vs. baseline and placebo, as measured by St. George's Respiratory Questionnaire (SGRQ). No statistically significant differences were observed in COPD Assessment Test (CAT)/SGRQ/Evaluating Respiratory Symptoms (E-RS) responder proportions vs. placebo (21, 22).
 - Exacerbations were consistently reduced across subgroups, regardless of airflow obstruction (Global Initiative for Chronic Obstructive Lung Disease [GOLD] Stage 2–4), COPD phenotype, varying treatment durations, cardiovascular (CV) comorbidities, prior severe exacerbations, and COPD duration (21, 22).
- **The pooled modified intention-to-treat (mITT)-300 population combined all mITT MATINEE participants and the BEC ≥ 300 cells/ μ l at screening subgroups from METREX and METREO (27).**
 - Mepolizumab significantly reduced the annualised rate of moderate/severe exacerbations by 21% (RR 0.79 [95% CI: 0.68, 0.91]; $p=0.002$) vs. placebo (27).
 - The time-to-first event analysis demonstrated the probability of having a moderate or severe exacerbations was lower with mepolizumab than placebo (Week 104 HR: [REDACTED]) (27).
 - Mepolizumab nominally significantly reduced the annualised rate of exacerbations leading to ED visits and/or hospitalisations by 29% (RR 0.71 [95% CI 0.51, 0.98]; $p=0.038$) vs. placebo (27).
 - Mepolizumab numerically improved QoL vs. baseline and placebo, as measured by SGRQ (27).

- **The comparative efficacy of mepolizumab vs. dupilumab has been evaluated via an indirect treatment comparison (ITC).**
 - Whilst mepolizumab demonstrated benefits in a wider spectrum of COPD patients compared to the dupilumab trials, to ensure a robust comparison, a matching-adjusted indirect comparison (MAIC) was conducted where the mepolizumab trial population was restricted to match the inclusion criteria of BOREAS/NOTUS (e.g. patients with symptoms of CB, modified Medical Research Council [mMRC] ≥ 2 , GOLD 2-3, BEC ≥ 300 at screening). CB was defined based on investigator assessment and SGRQ responses at baseline (166).
 - The MAIC of mepolizumab vs. dupilumab showed no statistically significant differences in reducing the risk of exacerbations and improving health-related quality of life (HRQoL) in overlapping trial populations. Favourable and comparable numerical trends were observed across various exacerbation outcomes:
 - For time to first moderate/severe exacerbation, HRs numerically favoured mepolizumab under both CB definitions analysed in the MAIC (investigator-defined CB HR: 0.71 [95% CI: 0.46, 1.08]; SGRQ-C-defined CB: HR 0.83 [95% CI: 0.61, 1.14])(166).
 - In the population with investigator-defined CB, mepolizumab had a numerically lower annualised rate of moderate/severe exacerbations (RR 0.91 [95% CI: 0.60, 1.37]) and severe exacerbations (RR 0.68 [95% CI: 0.27, 1.72]). In the population where CB was defined by SGRQ-C, the RRs for annualised rate of moderate/severe exacerbations and severe exacerbations were 1.13 (95% CI: 0.80, 1.58) and 1.01 (95% CI: 0.47, 2.16), respectively (166).
 - **Mepolizumab is administered once every four weeks (Q4W) (28), compared with once every two weeks (Q2W) for dupilumab (29), potentially aligning with patient preferences for treatments with lower frequency of use (30) and reducing treatment burden and supporting adherence (31, 32).**
- **Mepolizumab has an established safety profile across approved indications, studied for up to 10 years in both clinical trials and in the real world (33). The incidence of any adverse events (AE) and serious adverse events (SAE) was similar between mepolizumab- and placebo-treated patients with COPD (23, 24, 34). The safety of mepolizumab in COPD is consistent with its known benefit:risk profile.**

2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify relevant clinical evidence on the efficacy and safety of mepolizumab and relevant comparators for the treatment of patients with COPD with an eosinophilic phenotype. Full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated are provided in Appendix B.

Searches were initially carried out in MEDLINE, Embase, and CENTRAL on 14th October 2016, and were subsequently updated on 10th August 2018 (2018 SLR update), 21st June

2024 (2024 SLR update), and 18th August 2025 (2025 SLR update). In total, the SLR identified 120 publications plus one CSR reporting on 65 randomised controlled trials (RCTs). These included comparisons of ICS-based triple therapy vs. mono-, dual-, or alternative triple regimens, as well as studies assessing add-on therapies (e.g. azithromycin, mepolizumab, dupilumab, tezepelumab, itepekimab, benralizumab, tozorakimab, mitiperstat, astegolimab, theophylline, and roflumilast) administered alongside dual or ICS-based triple therapy. Of these, three Phase 3 RCTs (METREX (23, 24, 34), METREO (23, 25, 34), and MATINEE (21, 22)) evaluated mepolizumab 100 mg Q4W added to ICS-based triple therapy, in patients with moderate-to-very severe COPD, blood eosinophilic inflammation, and a history of frequent exacerbations. An additional Phase 2b randomised trial was identified (COPD-HELP) which assessed mepolizumab in a post-hospitalisation COPD population with an eosinophilic phenotype (167). Two Phase 3 RCTs (BOREAS (168, 169) and NOTUS (170, 171)) evaluated dupilumab 300 mg SC Q2W added to ICS-based triple therapy, in patients with moderate-to-severe COPD, CB symptoms, BEC ≥ 300 cells/ μ l, and a documented history of high exacerbation risk. A full list of included studies and summary study characteristics are provided in Appendix B. A summary of the mepolizumab evidence and corresponding primary and secondary publications is provided in Table 4.

Table 4: Summary of available clinical effectiveness evidence of mepolizumab

Trial	Sections	Referred to as	Study reference(s)
MATINEE (NCT04133909)	Section 2.3.1.1, Section 2.3.2.1, Section 2.4.1, Section 2.6.1, Appendix J	MATINEE	- Published: Scirba 2025 ; Papi 2025a (172); Criner 2025[¶] ATS (173); Bafhadel 2025[¶] ATS (174); Han 2025[¶] ATS (175); Jones 2025[¶] ATS (176); Pavord 2025[¶] ATS (177); Roche 2025[¶] ATS (178); Noorduynd 2025[¶] ATS (179); Papi 2025b[¶] ATS (180) Vogelmeier 2025[¶] ATS (181) - Unpublished: MATINEE CSR (21)
METREX (NCT02105948) (MEA117106)	Appendix J (efficacy), Section 2.11.2 (safety)	METREX	- Published: Pavord 2017 (23) - Unpublished: METREX CSR (24)
METREO (NCT02105961) (MEA117113)	Appendix J (efficacy), Section 2.11.2 (safety)	METREO	- Published: Pavord 2017 (23) - Unpublished: METREO CSR (25)
METREO + METREX pooled analyses	Appendix J (efficacy only)	Pooled eosinophilic population; reports some data for mITT-300 population from	Published: Pavord 2021 (34); Vogelmeier 2024 (182)

Trial	Sections	Referred to as	Study reference(s)
		METREO and METREX	
MATINEE mITT + METREX mITT-300[†] + METREO mITT-300[†] pooled analysis[‡]	Section 2.3.1.3, Section 2.3.2.3, Section 2.4.3, Section 2.6.3 (supplementary information in Appendix J)	mITT-300	Unpublished: Data on File (Module 2.7.3 Summary of Clinical Efficacy (27))
Supporting evidence			
COPD-HELP (NCT04075331) [§]	Appendix J	COPD-HELP	Published: Flynn 2025 (167)

Notes: Trials in **bold** represent the core evidence package for clinical effectiveness of mepolizumab SC vs. placebo in the target population (adults with uncontrolled COPD (defined as ≥ 2 moderate or ≥ 1 severe exacerbations within 12 months) of an eosinophilic phenotype (defined as ≥ 300 cells/ μ L at screening) on a combination of an ICS, a LABA, and a LAMA).

[†]From the mITT population only participants with BEC ≥ 300 cells/ μ L at screening who received ≥ 1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline were in the target population for this submission; [‡]A broader pooled population was created to support the economic model, incorporating IPD from two additional GSK-sponsored studies: IMPACT (Lipson, 2018 (183)), which was identified in the SLR (see Appendix B), and ECLIPSE (Vestbo, 2008 (184)), an observational study not captured by the RCT-focused SLR but included due to IPD availability. These were used alongside placebo (SoC) arms from MATINEE and the BEC ≥ 300 subgroup of METREX and METREO to inform the SoC arm in the model. Only the mepolizumab trials were used to estimate treatment effects mepolizumab vs. placebo (SoC) and, as such, this analysis is not discussed further in this section; [¶]Note conference abstracts not identified in the SLR due to search date cut-off, the conference abstract was provided by GSK; [§]Compared with MATINEE, this population was substantially more severe, with poorer lung function, higher symptom burden, and greater comorbidity. As such, COPD-HELP is not considered part of the core evidence package for this appraisal but is acknowledged as supportive. Abbreviations: ATS, American Thoracic Society; BEC, blood eosinophil count; COPD, Chronic Obstructive Pulmonary disease; CSR, clinical study report; ICS, inhaled corticosteroids; LABA, long-acting beta₂-agonist; LAMA, long-acting muscarinic antagonist; mITT-300, modified intention-to-treat 300 (participants with BEC ≥ 300 cells/ μ L at screening who received ≥ 1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline); RCT, randomised controlled trial; SC, subcutaneous; SLR, systematic literature review; SoC, standard of care.

2.2 List of relevant clinical effectiveness evidence

The Phase 3 global clinical programme comprised three randomised, double-blind, placebo-controlled trials evaluating mepolizumab 100 mg SC injection Q4W (hereafter referred to as mepolizumab) in patients with uncontrolled COPD of an eosinophilic phenotype on a combination of an ICS, a LABA, and a LAMA).

MATINEE (21, 22) was a multicentre, parallel-group trial that prospectively enrolled patients with T2 inflammation, defined by an eosinophilic phenotype (BEC ≥ 300 cells/ μ L at screening and ≥ 150 cells/ μ L within the previous 12 months), and a history of ≥ 2 moderate or ≥ 1 severe exacerbation(s) in the prior year. Participants received mepolizumab or placebo Q4W for 52–104 weeks in addition to triple inhaled therapy (ICS + LABA + LAMA). The trial examined efficacy across a broad COPD population, including patients with CB or emphysema and disease severity spanning GOLD Stages 2 to 4.

METREX (23, 24) was a parallel-group trial in patients with COPD and a history of ≥ 2 moderate or ≥ 1 severe exacerbation(s) in the prior year despite triple therapy. Participants were stratified

Company evidence submission for mepolizumab for treating chronic obstructive pulmonary disease with an eosinophilic phenotype [ID1237]

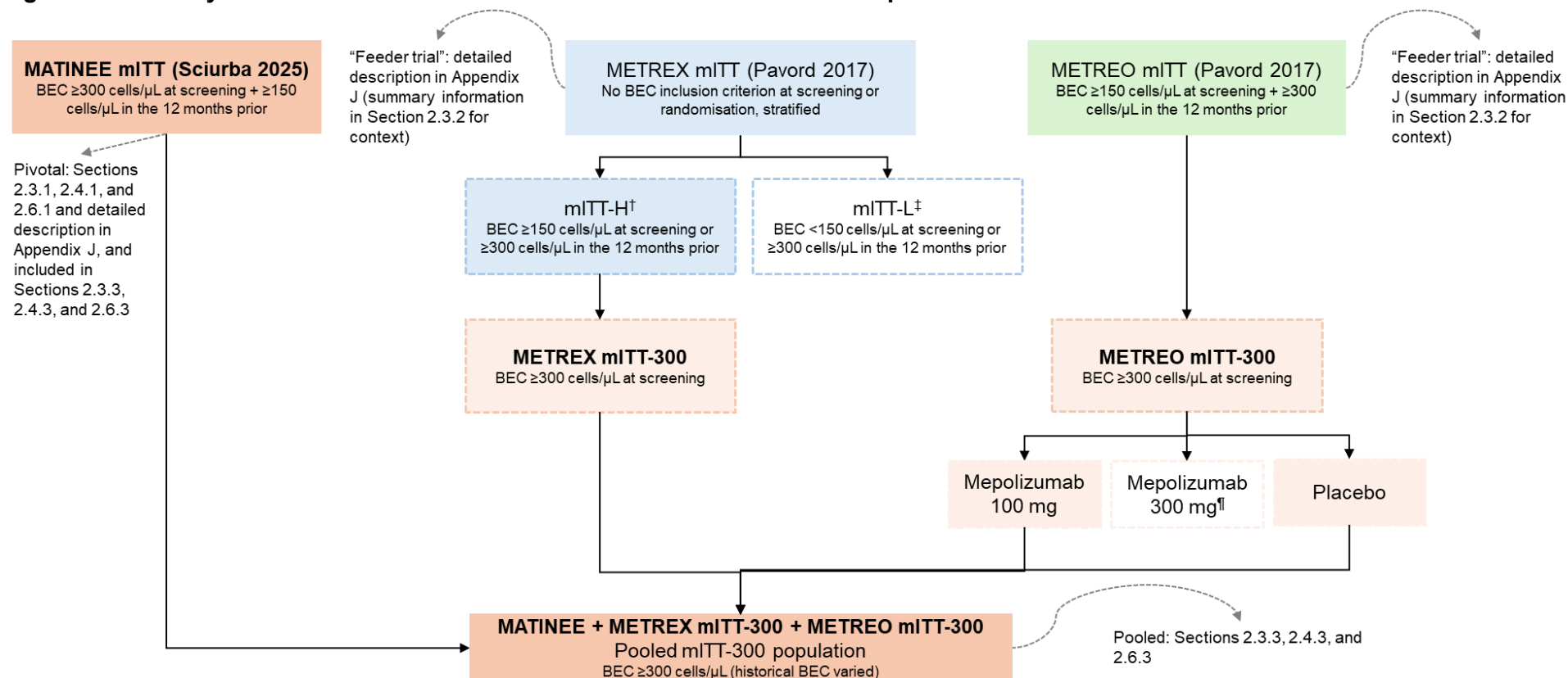
at randomisation by BEC: high stratum, BEC ≥ 150 cells/ μ L at screening or ≥ 300 cells/ μ L in the preceding 12 months and low stratum: BEC < 150 cells/ μ L at screening and no evidence of BEC ≥ 300 cells/ μ L in the preceding 12 months. METREO (23, 25) had similar eligibility criteria to METREX, but only enrolled participants meeting BEC criteria for the high stratum (BEC ≥ 150 cells/ μ L at screening or ≥ 300 cells/ μ L in the preceding 12 months). Participants were randomised to receive mepolizumab SC, mepolizumab 300 mg SC, or placebo Q4W for 52 weeks.

MATINEE reflects the population aligned with the scope of this appraisal – frequent exacerbations despite triple inhaled therapy, and BEC ≥ 300 cells/ μ L at screening and ≥ 150 cells/ μ L in the previous year. METREX (23, 24) and METREO (23, 25) included a subgroup of patients with BEC ≥ 300 cells/ μ L at screening (hereafter referred to as the modified intention-to-treat [mITT]-300 population). A pooled analysis has been performed (Section 2.4.3) which includes the MATINEE mITT population, and the mITT-300 populations from METREX and METREO, collectively termed the pooled mITT-300 population (27).

Beyond these Phase 3 trials, additional supportive evidence is available from COPD-HELP (Flynn *et al.*, 2025 (167)), a Phase 2b trial in patients hospitalised with a severe acute exacerbation of COPD and eosinophilic inflammation. Eligibility required age ≥ 40 years, ≥ 10 pack-years smoking history, treatment with inhaled corticosteroids, and a BEC ≥ 300 cells/ μ L either at the time of admission or within the preceding 12 months. The mean of the highest recorded BEC in the prior year was 570 cells/ μ L in both groups, whereas the geometric mean at randomisation was lower (150 cells/ μ L mepolizumab; 130 cells/ μ L placebo), likely reflecting transient suppression following systemic corticosteroid use during the index admission. This distinction matters because it shows that patients were selected for an eosinophilic phenotype even though their eosinophil counts were temporarily reduced when they entered the study. Compared with MATINEE, the COPD-HELP population was older and more comorbid (mean age 69 years, median of four comorbidities, 36% with CV disease, and highly impaired HRQoL at baseline (mean SGRQ-C total score ~ 71). Compared with trials of other biologics (21, 22, 168, 170), participants had a substantially higher recent exacerbation burden (mean 5.3 exacerbations in the prior year) more mean hospitalisations during follow-up (1.66), were more symptomatic, with a mean SGRQ-C of 70.9 and a median of four comorbidities, and had a mean highest BEC of ~ 570 cells/ μ L. While COPD-HELP is not considered part of the core evidence package, it provides supportive evidence for the appraisal (Appendix J).

Figure 6 provides an overview of the core clinical evidence sources relevant to the target population for this appraisal. A summary of key trial characteristics is provided in Section 2.3 (Table 5).

Figure 6: Summary of clinical effectiveness evidence relevant to the decision problem



Source: MATINEE CSR (21); Sciurba 2025 (22); METREX CSR (24); METREO CSR (25); Pavord 2017 (23); Pavord 2021 (reports some data for pooled METREX mITT-300 and METREO mITT-300 (34); Data on File (pooled mITT-300 pooled analysis) (27); Data on File (broader pooled analysis [pooled mITT-300 + IMPACT + ECLIPSE]) (26).

†A subset of the mITT population, consisting of all participants with BEC ≥150 cells/μL at screening or ≥300 cells/μL in the prior year; ‡A subset of the mITT population, consisting of all subjects with BEC <150 cells/μL at screening and no evidence of BEC ≥300 cells/μL in the prior year; ¶Mepolizumab 300 mg dose not in scope of this appraisal, licensed dose mepolizumab 100 mg/

Abbreviations: BEC, blood eosinophil count; CSR, clinical study report; ICS, inhaled corticosteroid; LABA, long-acting beta₂-agonist; LAMA, long-acting muscarinic antagonist; mITT, modified intention-to-treat; mITT-300 modified intention-to-treat 300 (participants with BEC ≥300 cells/μL at screening who received ≥1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline); mITT-H modified intention-to-treat high stratum; mITT-L, modified intention-to-treat low stratum; SG, subgroup.

Table 5: Summary of clinical effectiveness evidence relevant to the decision problem

Study	MATINEE (NCT04133909) mITT	METREX (NCT02105948) mITT [†]	METREO (NCT02105961) mITT [†]	MATINEE mITT + METREO mITT-300 + METREX mITT-300 (pooled mITT-300 population) ^{†††}
Study design	Phase 3, multicentre, randomised, double-blind, placebo-controlled trial. Duration was variable (≥52 to ≤104 weeks), with extension allowed following protocol amendment due to COVID-19.	Phase 3 randomised, double-blind, placebo-controlled trial. Fixed 52-week duration.	Phase 3, randomised, double-blind, placebo-controlled trial. Fixed 52-week duration.	Pooled analysis of IPD from three Phase 3, randomised, double-blind, placebo-controlled trials ^{†††}
Population	- Adults with moderate-to-very severe COPD (GOLD 2–4) with type 2 inflammation (BEC ≥300 cells/μL at screening and documented historical BEC ≥150 cells/μL in prior 12 months) ≥2 moderate exacerbations (systemic corticosteroids ± antibiotics) or ≥1 severe exacerbation (hospitalisation >24h) in prior 12 months. - Stable ICS-based triple therapy for ≥3 months - Current or former smokers (≥10 pack-years)	- Adults with moderate-to-very severe COPD (GOLD 2–4) ≥2 moderate exacerbations (systemic corticosteroids and/or antibiotics) or ≥1 severe exacerbation (hospitalisation) in prior 12 months - Stable ICS-based triple therapy for ≥3 months - No eosinophil threshold requirement for enrolment. Randomised with stratification by BEC - High stratum: BEC ≥150 cells/μL at screening or ≥300 cells/μL in prior 12 months	- Adults with moderate-to-very severe COPD (GOLD 2–4) with type 2 inflammation (BEC ≥150 cells/μL at screening or ≥300 cells/μL in prior 12 months)[‡] ≥2 moderate exacerbations (systemic corticosteroids ± antibiotics) or ≥1 severe exacerbation (hospitalisation) in prior 12 months - Stable ICS-based triple therapy for ≥3 months Exclusion: Current diagnosis of asthma (current or former smokers), diagnosis of	Combined from MATINEE mITT and ≥300 cells/μL at screening subgroups from METREX and METREO (referred to as the pooled mITT-300 population)

Company evidence submission for mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237]

Study	MATINEE (NCT04133909) mITT	METREX (NCT02105948) mITT [†]	METREO (NCT02105961) mITT [†]	MATINEE mITT + METREO mITT-300 + METREX mITT-300 (pooled mITT-300 population) ^{†††}
	Exclusion: Current, past, history or concurrent diagnosis of asthma (regardless of whether they had active or inactive disease)	– Low stratum: BEC <150 cells/μL Exclusion: Current diagnosis of asthma (current or former smokers), diagnosis of asthma at any time never smokers)	asthma at any time never smokers)	
Intervention(s)	Mepolizumab (SC) 100 mg/mL administered Q4W along with SoC	Mepolizumab (SC) 100 mg/mL administered Q4W along with SoC	- Mepolizumab (SC) 100 mg/mL administered Q4W along with SoC (primary comparison of interest) - Mepolizumab (SC) 300 mg/mL administered Q4W along with SoC therapy^{††}	Mepolizumab (SC) 100 mg/mL administered Q4W along with SoC
Comparator(s)	Placebo (0.9% sodium chloride) (SC) Q4W + SoC	Placebo (0.9% sodium chloride) (SC) Q4W + SoC	Placebo (0.9% sodium chloride) (SC) Q4W + SoC	Placebo (0.9% sodium chloride) (SC) Q4W + SoC
Indicate if study supports application for marketing authorisation	Yes	Yes	No	No
Indicate if study used in the economic model	Yes	Partly	Partly	Yes – used to estimate the treatment effect for mepolizumab in the economic model ^{§§§}
Rationale if study not used in model	NA	mITT-300 subgroup (BEC $\geq$ 300 cells/ μ L at screening) data were included in the pooled mITT-300 population for treatment effect as most	mITT-300 subgroup (BEC $\geq$ 300 cells/ μ L at screening) data were included in the pooled mITT-300 population for treatment effect as most	NA

Company evidence submission for mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237]

Study	MATINEE (NCT04133909) mITT	METREX (NCT02105948) mITT [†]	METREO (NCT02105961) mITT [†]	MATINEE mITT + METREO mITT-300 + METREX mITT-300 (pooled mITT-300 population) ^{†††}
		closely aligned with the target population; the full mITT population was not used	closely aligned with the target population; the full mITT population was not used	
Reported outcomes specified in the decision problem	Primary endpoint: - Annualised rate of moderate/severe exacerbations[§] up to Week 104 Secondary endpoints: - Time to first moderate/severe exacerbation - Proportion of CAT responders^{††} - Proportion of E-RS:COPD responders^{††} - Proportion of SGRQ-C responders^{†††} - Annualised rate of exacerbations requiring ED visit and/or hospitalisation - Safety including mortality (all cause including respiratory and cardiovascular causes of death) and discontinuation Additional/other efficacy endpoints were assessed, including:	Primary endpoint - Annualised rate of moderate/severe exacerbations[§] up to Week 52 Secondary endpoints: - Time to first moderate/severe exacerbation - Annual rate of COPD exacerbations requiring ED visit and/or hospitalisations - CFB mean SGRQ-C total score (secondary efficacy endpoint) - CFB CAT score (secondary endpoint) Other and additional efficacy endpoints were assessed, including: - Exacerbations (frequency of severe events [on- and off-treatment], including re-hospitalisations within 30 days); - Symptoms (rescue medication use; CAT	Primary endpoint - Annualised rate of moderate/severe exacerbations[§] up to Week 52 Secondary endpoints: - Time to first moderate/severe exacerbation - Annual rate of COPD exacerbations requiring ED visit and/or hospitalisations - CFB mean SGRQ-C total score (secondary efficacy endpoint) - CFB CAT score (secondary endpoint) Other and additional efficacy endpoints were assessed, including: - Exacerbations (frequency of severe events, including re-hospitalisations within 30 days); - Symptoms (rescue medication use; CAT	- Annualised rate of moderate/severe exacerbations[§] - Time to first moderate/severe exacerbation - Annualised rate of exacerbations requiring ED visit/hospitalisation - Time to first exacerbation requiring ED visit/hospitalisation - Proportion of participants with at least one exacerbation requiring ED visit/hospitalisation - Annualised rate of severe exacerbations - Time to first severe exacerbation - Proportion of participants with at least one severe exacerbation - Proportion of CAT responders^{††} - CFB CAT score - Proportion of SGRQ responders^{†††}

Company evidence submission for mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237]

Study	MATINEE (NCT04133909) mITT	METREX (NCT02105948) mITT [†]	METREO (NCT02105961) mITT [†]	MATINEE mITT + METREO mITT-300 + METREX mITT-300 (pooled mITT-300 population) ^{†††}
	- Exacerbations (time-to-first requiring ED-visit or hospitalisation [Week 104]; annualised frequency of severe [Week 104]; proportion of patients with ≥1 severe; time-to-first severe; annualised rate of moderate/severe by treatment type [Week 104]) - Lung function: CFB in pre-bronchodilator FEV₁ and FVC [Week 52] - HRQoL: CFB in EQ-5D-3L index score and VAS - HCRU associated with exacerbation to Week 104	- responders [≥2-point improvement]); - Lung function: CFB in trough FEV₁ and FVC; proportion with ≥100 mL FEV₁ increase); - HRQoL: (SGRQ domain scores and responder rates [≥4-point improvement]; EQ-5D-5L scores); - HCRU associated with exacerbation	- responders [≥2-point improvement]); - Lung function: CFB in trough FEV₁ and FVC; proportion with ≥100 mL FEV₁ increase); - HRQoL: (SGRQ domain scores and responder rates [≥4-point improvement]; EQ-5D-5L scores) - HCRU associated with exacerbation	- CFB SGRQ score - SGRQ domain scores
All other reported outcomes	HCRU (hospitalisations [length of stay; exploratory, recall-based])	HCRU (hospitalisations [length of stay; exploratory, recall-based])	HCRU (hospitalisations [length of stay; exploratory, recall-based])	

Source: MATINEE CSR (21); METREX CSR (24) [Pavord 2017 (23)]; METREO CSR (25) [Pavord 2017 (23)];]Data on File (pooled mITT-300 population) (27); Pavord 2021 (34) (includes pooled METREO mITT-300 and METREX mITT-300 analysis).

[†]Details of the individual METREX and METREO trials are provided in Appendix J. As noted in Figure 6, these trials are “feeder trials” for the pooled analysis;

[‡]The BEC criterion was a randomisation criterion applied at Visit 2 (Appendix J); [¶]The mepolizumab 300 mg dose is not in scope of the decision problem, the mepolizumab SC dose is the anticipated licensed dose; [§]Moderate: leading to treatment with systemic glucocorticoid, antibiotic, or both; Severe: leading to hospitalisation or resulting in death; ^{††}CAT is an 8-item questionnaire used to measure the health status of patients with COPD, participants rate their experience a 6-point scale, ranging from 0 (no impairment) to 5 (maximum impairment) with a scoring range of 0–40. Higher scores indicate greater disease impact; ^{†††}E-RS:COPD consisted of 11 items from the 14 item EXACT instrument (completed each evening using an eDiary). E-RS:COPD was intended to capture information related to the respiratory symptoms of COPD, i.e., breathlessness, cough, sputum production, chest congestion, and chest tightness. The E-RS:COPD had a

Company evidence submission for mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237]

scoring range of 0-40, higher scores indicate more severe symptoms. Three sub-scales of the E-RS:COPD were used to describe different symptoms (breathlessness, cough and sputum, and chest symptoms); ¶¶SGRQ-C is a 40-item questionnaire. A total score and 3 component scores, a Symptoms score, Activity score and Impacts score were calculated based on the scoring algorithm detailed in the SGRQ-C Manual Version 1.3. The total score was expressed as a percentage of overall impairment with 100 representing the worst possible health status and 0 the best possible health status. Higher scores indicate greater impairment of health; §§Healthcare resource collected unscheduled use of health care resources throughout the study period and included number and duration of medical encounters (e.g., surgeries, hospitalisations by ward type, outpatient visits, emergency care, home visits), tests, procedures, medications, and long-term oxygen therapy. Recorded in a worksheet by participants and added to the eCRF by investigator and study-centre staff; †††The mITT-300 analysis includes data from the mepolizumab trials (MATINEE and the BEC ≥300 subgroup from METREX and METREO)

Abbreviations: BEC, blood eosinophil count; CAT, COPD assessment test; CB, chronic bronchitis; COPD, chronic obstructive pulmonary disease; eCRF, electronic case report form; ED, emergency department; E-RS:COPD, Evaluating Respiratory Symptoms in COPD; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; FP, fluticasone propionate; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HCRU, healthcare resource use; HRQoL, health-related quality of life; ICS, inhaled corticosteroid; ICU, intensive care unit; IPD, individual patient data; LABA, long-acting β₂-agonist; LAMA, long-acting muscarinic antagonist, mITT, modified intention-to-treat; mITT-300 modified intention-to-treat 300 (participants with BEC ≥300 cells/μL at screening who received ≥1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline); mMRC, modified Medical Research Council; NA, not applicable; Q4W, once every 4 weeks; SC, subcutaneous; SG, subgroup; SGQR-C, St. George's Respiratory Questionnaire – COPD specific version; SoC, standard-of-care; VAS, visual analogue score.

2.3 Summary of methodology of the relevant clinical effectiveness evidence

2.3.1 Study methodology

2.3.1.1 MATINEE

The study design and methods for the MATINEE trial (21, 22) is provided in Table 6.

Table 6: Study design and methods

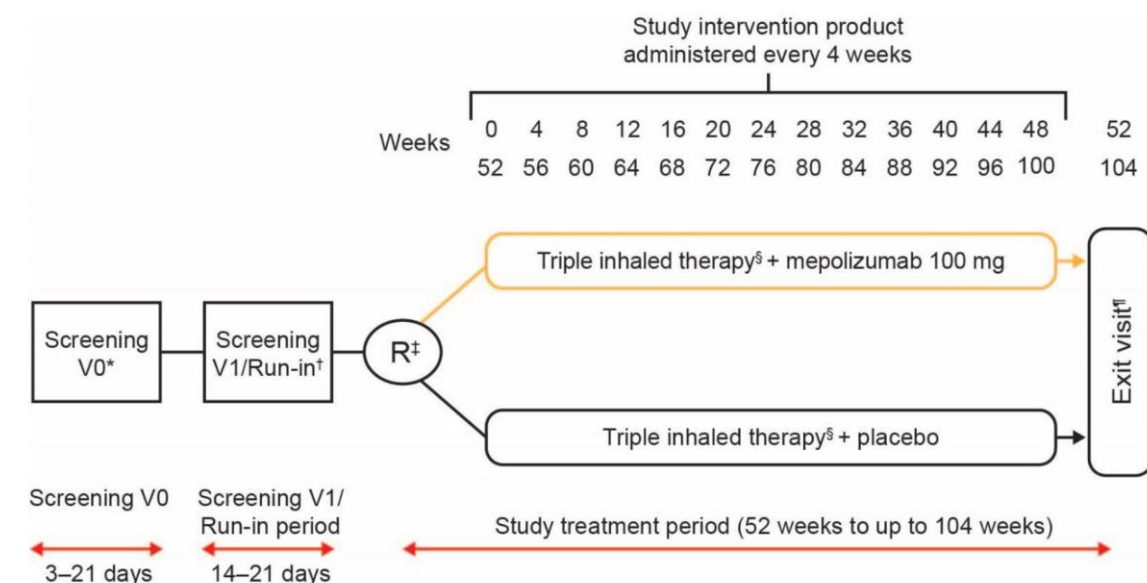
Trial	MATINEE (MAT208657) (NCT04133909)
Location	Multinational study conducted across Asia (China, Republic of South Korea, Taiwan), Europe (Belgium, Denmark, France, Germany, Greece, Ireland, Italy, Netherlands, Spain, Sweden, UK), Eastern Europe (Hungary, Poland), North America (Canada, USA), South America (Argentina, Brazil, Mexico), and Rest of World (Australia, India, Israel and New Zealand).
Trial design	The objective of the MATINEE study was to evaluate the efficacy and safety of mepolizumab as an add-on treatment in participants with COPD with elevated blood eosinophil levels and at risk of exacerbations despite optimised inhaled therapy (22). MATINEE is a Phase 3, multicentre, randomised, placebo-controlled, double-blind, parallel-group study with a variable study duration of at least 52 weeks and up to 104 weeks. Patients were recruited across 25 countries from October 2019 to August 2024, recruitment was paused from March and June 2020 due to the COVID-19 pandemic

(22). Following a 2-week run-in period designed to evaluate comprehension and adherence to the eDiary, eligible participants were randomised 1:1 to receive at least 52 weeks of one of the following treatments:

- Mepolizumab 100 mg SC Q4W
- Placebo SC Q4W

Patients continued to receive their optimised maintenance COPD therapy throughout the study duration, irrespective of the treatment assignment (22). A study design schematic for MATINEE is provided in Figure 7.

Figure 7: MATINEE study design schematic



The 2-week run-in period assessed compliance with daily electronic diary use. *Patients were required to have BEC ≥ 300 cells/ μ L at Screening Visit 0 to proceed to Visit 1, alongside a documented historical BEC ≥ 150 cells/ μ L in the 12 months prior to Screening Visit 0. †Patients with no historical BEC ≥ 150 cells/ μ L were required to have BEC ≥ 150 cells/ μ L at Screening Visit 1. ‡R = randomisation; randomisation criteria were assessed at Week 0 (Visit 2), prior to randomisation. §Patients were required to use an ICS-based triple therapy (fluticasone propionate ≥ 500 μ g/day dose or equivalent plus LABA, and LAMA) unless documentation of safety or intolerance issues related to LABA or LAMA. ¶For patients enrolled in the study for 52 weeks, the exit visit was at Week 52; for patients receiving study treatment beyond 52 weeks, the exit visit was at Week 104 or aligned to the date the last randomised patient was scheduled to complete their Week 52 exit visit (whichever was sooner); in all cases, the exit visit was 4 weeks after the last dose. Abbreviations: BEC, blood eosinophil count; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; V, visit.

Study completion	The study was designed to collect data after premature discontinuation of treatment. Participants were considered to have completed the study if they met the following criteria, regardless of premature discontinuation of the study treatment. Participants enrolled for 52 Weeks: A participant was considered to have completed the study if they continued to participate in the study until the Exit Visit at Week 52. Participants enrolled beyond 52 Weeks (or reconsented to continue beyond 52 Weeks and up to 104 Weeks): A participant was considered to have completed the study if they continued to participate in the study until the earlier of: the Exit Visit at Week 104 OR a scheduled visit that was on or immediately before the date of the Exit Visit at Week 52 of the last participant to have been randomised into the study. By study design, the duration of study varied for the participants enrolled beyond 52 weeks (or reconsented to continue beyond 52 weeks).
Eligibility criteria for participants	Inclusion criteria This study enrolled male or female (not pregnant/breastfeeding; not of childbearing potential, or using a highly effective contraceptive method per protocol) participants ≥ 40 years of age who were current or former cigarette smokers with a history of ≥ 10 pack-years at Screening (Visit 1) and who met the following criteria: • Blood eosinophils: A peripheral BEC of ≥ 300 cells/μL from the haematology sample collected at Screening Visit 0 AND a documented historical BEC of ≥ 150 cells/μL in the 12 months prior to Screening Visit 0 that met the following: it had to be measured between 12 months and one month prior to Visit 0, and it must not have been measured within 14 days of a COPD exacerbation. Participants with no documented historical BEC of ≥ 150 cells/μL must meet this threshold based on the Screening Visit 1 assessment to return for Randomisation at Visit 2. COPD diagnosis and severity: A clinically documented history of COPD for at least 12 months, characterised as moderate-to-very-severe disease (GOLD stages 2 to 4) in accordance with the definition by the ATS/ERS (185). Patients could have CB, emphysema, or both. Participants had to present with the following: ○ A measured pre- and post-salbutamol FEV₁/FVC ratio of < 0.70 at Screening Visit 1 to confirm the diagnosis of COPD. ○ A measured post-salbutamol FEV₁ $> 20\%$ and $\leq 80\%$ of predicted normal values calculated using NHANES III reference equations (186, 187) at Screening Visit 1. • History of exacerbations: Participants had to have a well-documented history (e.g., medical record verification) in the 12 months prior to Screening Visit 1 of: ○ Two or more moderate COPD exacerbations that were treated with systemic corticosteroids (IM, IV, or orally) with or without antibiotics OR ○ at least one severe COPD exacerbation requiring hospitalisation Note: At least one exacerbation had to have occurred while the participant was taking inhaled triple therapy, ICS + LABA + LAMA, unless documented intolerance or safety risk with either of the two long-acting bronchodilators. If intolerance was documented, ICS + LABA or ICS + LAMA would be allowable after discussion with the medical monitor.

	Note: COPD exacerbation(s) related to laboratory confirmed COVID-19 infection were not counted as COPD exacerbation(s) for inclusion in the study. • Concomitant COPD therapy: Participants had a well-documented requirement for optimised SoC background therapy that included ICS plus two additional COPD medications (i.e., ICS-based triple therapy) for the 12 months prior to Screening Visit 1 and met the following criteria: ○ Immediately prior to Screening Visit 1, minimum of three months of use of an a) ICS at a dose ≥ 500 mcg/day fluticasone propionate dose equivalent plus b) LABA, and c) LAMA unless documentation of safety or intolerance issues related to LABA or LAMA. ○ For participants who were not continually maintained on ICS + LABA + LAMA for the entire 12 months prior to Visit 1, use of the following was allowed (but not in the 3 months immediately prior to Visit 1): ▪ ICS at a dose ≥ 500 mcg/day fluticasone propionate dose equivalent plus ▪ Inhaled LABA or inhaled LAMA, and ▪ PDE-4-inhibitors, methylxanthines, or scheduled daily use of SABA and/or SAMA. • Note: Where intolerance or safety risk was documented for either LAMA or LABA, ICS-based inhaled dual maintenance therapy, either ICS + LABA or ICS + LAMA, was allowed in the 12 months prior to Visit 1 and during the clinical trial but could be discussed with the medical monitor. • Note: Participants had to be willing to receive optimised maintenance COPD therapy for the duration of the study. Exclusion criteria Participants who met any of the following criteria were excluded from the study: • Asthma: Participants with a past history or concurrent diagnosis of asthma were excluded regardless of whether they have active or inactive disease • Other respiratory disorders: The investigator had to judge that COPD was the primary diagnosis accounting for the clinical manifestations of the lung disease. Participants with $\alpha 1$-antitrypsin deficiency as the underlying cause of COPD were excluded. Also, participants with active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, primary pulmonary hypertension, ILDs or other active pulmonary diseases were excluded. • COPD stability: Participants with pneumonia, COPD exacerbation, or LRTI within the 4 weeks prior to Screening Visit 1. • Lung resection: Participants with lung volume reduction surgery within the 12 months prior to Screening Visit 1. • Pulmonary rehabilitation program: Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Screening Visit 1. Participants who were in the maintenance phase of a pulmonary rehabilitation program were not excluded.

	• Oxygen: Participants who received treatment with oxygen more than 2 L/min at rest over 24 hours. For participants receiving oxygen treatment, participants had to demonstrate an oxyhaemoglobin saturation greater than or equal to 89% while breathing supplemental oxygen.
Settings and locations where the data were collected	• A total of 3,306 participants were screened at 344 study centres in 25 countries. The countries with the highest number screened were the US (746; 23%), the UK (549; 17%), Germany (377; 11%), and Argentina (371; 11%).
Trial drugs	• SoC therapy plus add-on: ○ Mepolizumab 100 mg SC Q4W (n=403) ○ Placebo SC Q4W (n=401) Administered for 52 weeks as add-on to optimised SoC therapy. Optimised SoC required prior use of ICS-based triple therapy (ICS ≥ 500 μg/day fluticasone propionate equivalent + LABA + LAMA) for ≥ 3 months before screening. Where triple therapy was not maintained for 12 months, participants could qualify with ICS (≥ 500 μg/day) + LABA or LAMA + a third agent (e.g., PDE-4 inhibitor, methylxanthine, or scheduled SABA/SAMA), excluding the three months prior to screening.
Permitted and disallowed concomitant medication	• Concomitant therapy: All medications (prescription, over the counter, supplements, vaccines) used at screening or during the study were recorded with reason, start/end dates, dose, and frequency. COVID-19 vaccination with authorised vaccines was permitted; unapproved vaccines were prohibited. • Rescue medication: Participants were provided salbutamol (MDI or nebulas) as needed. Use was permitted throughout the study but should be avoided for at least four hours before spirometry. • Permitted COPD medications (if stable and per protocol): Included standard maintenance therapies such ICS, long-acting bronchodilators (muscarinic antagonists and beta₂-agonists), PDE-4 inhibitors, methylxanthines, chronic oral corticosteroids, leukotriene receptor antagonists, short-term corticosteroids and antibiotics for exacerbations, mucolytics, long-term oxygen therapy (≤ 2 L/min at rest), rescue bronchodilators (e.g., salbutamol), and maintenance-phase pulmonary rehabilitation (not initiated during the study). • Permitted non-COPD medications and therapies: Allowed treatments included intranasal therapies for rhinitis, topical and ophthalmic corticosteroids, localised corticosteroid injections, vaccines (e.g., influenza, pneumonia, shingles), allergy immunotherapy, short-term antibiotics for acute infections, beta-blockers, smoking cessation treatments, cough suppressants, antidepressants, anxiolytics, CPAP/BiPAP, and stable immunosuppressants for non-COPD conditions (with Medical Monitor approval). • Prohibited medications/therapies: Excluded therapies included the acute phase of pulmonary rehabilitation, long-term systemic antibiotic therapy, monoclonal antibodies, chronic oral corticosteroids for non-COPD indications, experimental anti-inflammatory or investigational products (within 30 days or 5 half-lives before Visit 1), and radiation therapy within 12 months prior to Visit 1 or during the study.

Primary outcomes (including scoring methods and timings of assessments)	Annualised rate of moderate/severe exacerbations measured from baseline (Visit 2) to Week 104 (Visit 28): • Moderate exacerbations: Defined as clinically significant exacerbations that required oral/systemic corticosteroids and/or antibiotics • Severe exacerbations: Defined as clinically significant exacerbations that required hospitalisation (≥24 hrs) or resulted in death
Other outcomes used in the economic model/specified in the scope	• Time to first moderate/severe exacerbation (from baseline to Week 104) (secondary endpoint) • Proportion of CAT responders (≥2-point improvement) at Week 52^{††} (secondary endpoint) • Proportion of SGRQ responders (defined as ≥4-point improvement in SGRQ total score [MCID] at Week 52) (secondary endpoint)^{††} • Proportion of E-RS:COPD responders (≥2-point improvement) at Weeks 49–52^{††} (secondary endpoint) • Annualised rate of exacerbations requiring ED visit and/or hospitalisation over 104 weeks (secondary endpoint) Safety • Incidence of AEs/SAEs including systemic reactions. • Incidence of adjudicated SAE reports and MACE events (CV death, non-fatal myocardial infarction, and non-fatal stroke) • Vital signs including BP, body temperature, pulse rate • ECG assessments • Mortality (all cause including respiratory and cardiovascular causes of death) • Presence of ADA to mepolizumab • Haematological and clinical chemistry parameters Additional/other efficacy and health outcome endpoints were assessed, including: • Exacerbations (time-to-first requiring ED-visit or hospitalisation [Week 104]; annualised frequency of severe [Week 104]; proportion of patients with ≥1 severe; time-to-first severe; annualised rate of moderate/severe by treatment type [Week 104]) • Lung function: CFB in pre-bronchodilator FEV₁ and FVC [Week 52] • HRQoL: CFB in EQ-5D-3L index score and VAS • HCRU associated with exacerbation to Week 104
Pre-planned and post-hoc subgroups	For the primary endpoint, a separate exploratory analysis within each of the below subgroup categories was carried out (refer to Table 11 for the approach to the analysis) • Age (<40 years, 40–<65 years, ≥65 years) • Sex (Male, Female) • Race (African American/African Heritage, White, Asian, Other)

	• Baseline BMI (kg/m²) (Low [≤ 20], Medium [$>20\text{--}\leq 30$], High [>30]) • Geographic Region (Europe, Eastern Europe, Asia, South America, North America, Rest of World)^{†‡} • Exacerbations in the previous year (≤ 2, 3, ≥ 4 exacerbations) • Severe exacerbations in the previous year (0, ≥ 1 exacerbation) • Screening blood eosinophil categories (<0.5 GI/L, ≥ 0.5 GI/L) • Smoking status at screening (Current, Former) • Symptoms of chronic bronchitis (Yes [based on SGRQ-C], No) • CV disease comorbidity (Any past or current cardiac condition) • mMRC Score at Screening (<2, ≥ 2) • Severity of airflow limitation (GOLD Reports) (Mild, Moderate, Severe, Very Severe) • Treatment duration^{¶¶} (Fixed Duration [52 weeks], Variable Duration [up to 104 weeks]) Exploratory analyses were conducted for select secondary endpoints within prespecified subgroups. • Screening blood eosinophil categories: Analyses for time to first moderate/severe exacerbation, CAT responders, and SGRQ responders. • Symptoms of chronic bronchitis and smoking status: Analyses for time to first moderate/severe exacerbation, CAT responders, SGRQ responders, and change from baseline in SGRQ. • Geographic region: Analyses for SGRQ responders and E-RS:COPD responders. Refer to Table 11 for the approach to the analysis. The post hoc programme spans phenotypes, disease severity, comorbidities, biomarkers, treatment durability, corticosteroid use, and patient-reported outcomes, as well as pooled and real-world evidence analyses to strengthen the case across subgroups and align with dupilumab comparators.

Source: MATINEE CSR (21); Sciurba 2025

[†]CAT is an 8-item questionnaire used to measure the health status of patients with COPD, participants rate their experience on a 6-point scale, ranging from 0 (no impairment) to 5 (maximum impairment) with a scoring range of 0-40. Higher scores indicate greater disease impact; [‡]E-RS:COPD consisted of 11 items from the 14 item EXACT instrument (completed each evening using an eDiary). E-RS:COPD was intended to capture information related to the respiratory symptoms of COPD, i.e., breathlessness, cough, sputum production, chest congestion, and chest tightness. The E-RS:COPD had a scoring range of 0-40, higher scores indicate more severe symptoms. Three sub-scales of the E-RS:COPD were used to describe different symptoms (breathlessness, cough and sputum, and chest symptoms); [¶]SGRQ-C is a 40-item questionnaire. A total score and 3 component scores, a Symptoms score, Activity score and Impacts score were calculated based on the scoring algorithm detailed in the SGRQ-C Manual Version 1.3. The total score was expressed as a percentage of overall impairment with 100 representing the worst possible health status and 0 the best possible health status. Higher scores indicate greater impairment of health; [§]Healthcare resource collected unscheduled use of health care resources throughout the study period and included number and duration of medical encounters (e.g., surgeries, hospitalisations by ward type, outpatient visits, emergency care, home visits), tests, procedures, medications, and long-term oxygen therapy. Recorded in a worksheet by participants and added to the eCRF by investigator and study-centre staff; ^{††}Proportion of responders also available at timepoint Week 24 but not reported in the submission or used in the economic model; ^{‡‡}Numbers of participants within the geographic regions

Company evidence submission for mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237]

are too small then regions may be further combined for analysis; ¶¶¶From Treatment Duration Confirmation eCRF page. For participants who completed the study prior to release of Protocol Amendment 6, no information was entered into this eCRF page retrospectively, all such patients were categorised as Fixed Duration

Abbreviations: ADA, anti-drug antibodies; AE, adverse event; ATS, American Thoracic Society; BEC, blood eosinophil count; BiPAP, Bi-Level Positive Airway Pressure; BMI, body mass index; CAT, COPD Assessment Test; CB, chronic bronchitis; COPD, chronic obstructive pulmonary disorder; COVID-19, coronavirus disease 2019; CPAP, Continuous Positive Airway Pressure; CV, cardiovascular; eCRF, electronic case report form; ECG, echocardiogram; ED, emergency department; E-RS:COPD, Evaluating Respiratory Symptoms in Chronic Obstructive Pulmonary Disorder; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HCRU, healthcare resource use; HRQoL, health-related quality of life; ICS, inhaled corticosteroid; ILD interstitial lung disease; IM, intramuscular; IV, intravenous; LABA, long-acting beta₂-agonist; LAMA, long-acting muscarinic antagonist; MACE, major adverse cardiac event; MCID, minimal clinically important difference; MDI, metered dose inhaler; mMRC, modified medical research council; NHANES, National Health and Nutrition Examination Survey; PDE-4, phosphodiesterase-4; Q4W, every 4 weeks; RTI, respiratory tract infection; SABA, short-acting beta₂-agonist; SAE, serious adverse event; SAMA, short-acting muscarinic antagonist; SC, subcutaneous; SGRQ-C, St. George's Respiratory Questionnaire – COPD specific version; SoC, standard of care; UK, United Kingdom; US, United States; VAS, visual analogue scale.

2.3.1.2 METREX and METREO

Two pivotal studies METREO (23, 25) and METREX (23, 24) were conducted concurrently and evaluated mepolizumab 100 mg (both studies) and 300 mg (METREO only) compared with placebo:

- METREX (23, 24) enrolled adults with moderate-to-very-severe COPD and a history of ≥ 2 moderate exacerbations in the past 12 months. Patients were required to be on ICS + LABA + LAMA at baseline. Randomisation was by eosinophil count: high stratum: ≥ 150 cells/ μ L at screening or ≥ 300 cells/ μ L within the 12 months prior and low stratum: < 150 cells/ μ L at screening and no evidence of ≥ 300 cells/ μ L within the 12 months prior). Further details on trial design are provided in Appendix J
- METREO (23, 25) enrolled adults with moderate-to-very-severe COPD and a history of ≥ 2 moderate exacerbations in the past 12 months. Patients were required to be on triple inhaled maintenance therapy (ICS + LABA + LAMA) at baseline. Eligible patients had to have T2 inflammation, defined as BEC ≥ 150 cells/ μ L at screening or ≥ 300 cells/ μ L in the prior 12 months. While METREO (23, 25) included a 300 mg mepolizumab treatment arm, this dose is not anticipated to be licensed for COPD (though it is licensed for other eosinophilic conditions such as hypereosinophilic syndrome and EGPA). The focus on the 100 mg dose reflects the anticipated licence and intended use in COPD. Further details on trial design are provided in Appendix J.

A detailed description of study methodology for the METREX (23, 24) and METREO (23, 25) trials (including for the pooled eosinophilic population [≥ 150 cells/ μ L at screening or ≥ 300 cells/ μ L within the 12 months prior] (34)) is provided in Appendix J (Section J.2 and Section J.3).

2.3.1.3 Pooled mITT-300 analysis (MATINEE [mITT], METREX [mITT-300] and METREO [mITT-300])

A pooled analysis of mepolizumab SC vs. placebo was conducted using data from the three Phase 3 trials, MATINEE (21, 22), METREX (23, 24), and METREO (23, 25). This pooled mITT-300 population (27) comprised all participants from MATINEE and participants from the METREX and METREO trials who:

- Had a BEC ≥ 300 cells/ μ L at screening;
- Were receiving SoC triple inhaled therapy (ICS + LABA + LAMA) at baseline;
- Met all study eligibility criteria for the respective trials; and

Company evidence submission for mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237]

- Received at least one dose of study treatment (mepolizumab 100 mg or placebo).

Together this analysis population is referred to as the pooled mITT-300 population(27). This population was defined to reflect the intended target group – adults with uncontrolled COPD of an eosinophilic phenotype despite treatment on a combination of an ICS and a LABA, and a LAMA. While the mITT-300 population(27) shares key clinical characteristics with MATINEE (21, 22), the BEC entry criteria in the original trials were broader: eligibility required BEC ≥ 150 cells/ μ L at screening or ≥ 300 cells/ μ L in the prior 12 months. Applying the ≥ 300 cells/ μ L at screening threshold post-hoc therefore captures a subgroup consistent with the patient population of MATINEE but may include some patients without a historical BEC ≥ 150 cells/ μ L. In practice, most with ≥ 300 cells/ μ L at screening are likely to meet the historical threshold, so the populations remain closely comparable. Other entry criteria differences included the exclusion of any asthma history (applied more consistently in MATINEE), and the definition of qualifying exacerbations (MATINEE required systemic corticosteroid use for moderate events). A summary of differences in study design between MATINEE and METREO and METREX trials is provided in Appendix J (Section J.4).

Taken together, the pooled mITT-300 population and MATINEE provide complementary and consistent evidence for the clinical effectiveness of mepolizumab in patients meeting these criteria. A summary of participant numbers in the pooled mITT-300 population is provided in Table 7.

Table 7: Summary of participants in the pooled mITT-300 population

Study ID	mITT population		Pooled mITT-300 [‡] population	
	Mepo n (%)	PBO n (%)	Mepo n (%)	PBO n (%)
MATINEE[†]	403 (39%)	401 (38%)	403 (71%)	401 (69%)
METREO[†]	223 (21%)	226 (22%)	83 (15%)	87 (15%)
METREX[†]	417 (40%)	419 (40%)	82 (14%)	90 (16%)
Total	1,043 (100%)	1,046 (100%)	568 (100%)	578 (100%)

Source: MATINEE CSR (21); Sciurba 2025 (22); METREX CSR (24); METREO CSR (25); Pavord 2017 (23); pooled mITT-300 pooled analysis (27)

[†]A full description of methods and results for individual trials is provided in Appendix J.

Abbreviations: CSR, clinical study report; ICS, inhaled corticosteroid; LABA, long-acting beta₂-agonist; LAMA, long-acting muscarinic antagonist; mepo, mepolizumab; mITT, modified intention-to-treat; mITT-300, modified intention-to-treat 300 (participants with BEC ≥ 300 cells/ μ L at screening who received ≥ 1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline); PBO, placebo.

2.3.2 Baseline characteristics

2.3.2.1 MATINEE

Demographics were generally balanced between treatment groups. The study population was predominantly White (84%) and male (69%), with a mean age of 66.2 years; 61% were aged ≥ 65 years. The mean BMI was 27.25 kg/m². The proportion of participants ≥ 65 years was slightly higher in the mepolizumab group (65%) compared with placebo (57%).

The mean duration of COPD was approximately 10 years, with most participants having moderate or severe airflow limitation, and 13–14% classified as very severe. The majority reported significant dyspnoea (mMRC ≥ 2) and poor HRQoL, as indicated by elevated CAT and SGRQ – COPD specific (SGRQ-C) scores. Nearly all participants met GOLD Group E criteria, reflecting high symptom burden and exacerbation risk. Screening BECs were elevated (geometric mean ~ 0.48 g/L) across both groups, consistent with a T2 inflammation phenotype. CV comorbidities were present in approximately 25%, and most had at least one non-CV comorbidity.

The mean ([standard deviation [SD]]) number of moderate/severe exacerbations in the 12 months prior to screening was 2.3 (1.10) in the mepolizumab group and 2.4 (1.15) in the placebo group. The majority experienced ≥ 2 events and about 20% had a severe exacerbation requiring hospitalisation. Inclusion criteria required that moderate exacerbations were treated with systemic corticosteroids.

Around two-thirds were former smokers, and one-third were current smokers. Among smokers, the mean (SD) pack-year history was 43.2 (25.99) in the mepolizumab group and 42.7 (23.74) in placebo. Baseline lung function was similar between groups, with pre-bronchodilator forced expiratory volume in one second (FEV₁) mean (SD) of 1,240.4 (482.04) mL (mepolizumab) and 1,281.8 (537.00) mL (placebo) and FVC of 2,595.6 (827.49) mL and 2,605.0 (782.47) mL, respectively.

Overall, the trial population of MATINEE reflects a wide spectrum of airflow obstructions (GOLD Stage 2–4), the full spectrum of mMRC scores (mMRC 0–4) and patients regardless of symptoms of CB or COPD phenotype (CB-only, emphysema-only, both or neither).

Summary baseline characteristics for the MATINEE trial are provided in Table 8.

Table 8: MATINEE: Participant baseline characteristics (mITT population)

Characteristic	Mepo (N=403)	PBO (N=401)
Age		
Mean (SD)	66.4 (8.10)	66.0 (7.91)

Company evidence submission for mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237]

Characteristic	Mepo (N=403)	PBO (N=401)
Median (min, max)	67.0 (39, 88)	66.0 (42, 91)
Age group years, n (%)		
<40	0	1 (<1)
40 to <65	142 (35)	173 (43)
≥65 years, n (%)	260 (65)	228 (57)
Sex, n (%)		
Female	127 (32)	126 (31)
Male	276 (68)	276 (68)
Ethnicity, n (%)		
Hispanic or Latino	94 (23)	95 (24)
Not Hispanic or Latino	309 (77)	306 (76)
Race, n (%)		
American Indian/Alaskan Native	3 (<1)	2 (<1)
Asian	56 (14)	56 (14)
Black or African American	5 (1)	5 (1)
Native Hawaiian or Other Pacific Islander	0	0
White	338 (84)	335 (84)
Mixed Race	1 (<1)	3 (<1)
Height (cm) mean (SD)	167.2 (8.98)	167.4 (9.34)
Weight (kg) mean (SD)	76.91 (17.970)	76.36 (17.964)
BMI kg/m² mean (SD)	27.38 (5.342)	27.13 (5.540)
Duration of COPD ≥10 years n (%)	156 (39)	151 (38)
Mean duration of COPD (years)	10.2 (6.65)	9.7 (5.88)
Severity of airflow limitation[†], n (%)		
Mild ≥80% predicted	2 (<1)	3 (<1)
Moderate: ≥50% <80% predicted	168 (42)	181 (45)
Severe: ≥30% <50% predicted	180 (45)	160 (40)
Very severe: <30%	53 (13)	57 (14)
CV comorbidity[‡], n (%)	103 (26)	97 (24)
Other comorbidity[¶], n (%)	318 (79)	323 (81)
mMRC score at screening, n (%)		
mMRC <2	93 (23)	98 (24)
mMRC ≥2	310 (77)	301 (75)
Missing	2 (<1)	4 (<1)
Ever diagnosed with GERD, n (%)	85 (21)	92 (23)

Characteristic	Mepo (N=403)	PBO (N=401)
GOLD Group E[§], n (%)	393 (98)	401 (>99)
Screening blood eosinophils, GI/L geometric mean (SD logs)	0.48 (0.378)	0.48 (0.398)
CAT total score^{††}, n; mean (SD)	389; 19.2 (6.95)	393; 19.1 (6.75)
SGRQ-C total score^{††}, n; mean (SD)	388; 55.3 (17.73)	392; 53.9 (17.86)
Number of moderate/severe exacerbations^{¶¶}, mean (SD)	2.3 (0.98)	2.2 (0.90)
Smoking history, n (%)		
Never smoker	0	0
Current smoker	111 (28)	111 (28)
Former smoker	292 (72)	290 (72)
Smoking pack years^{§§}, n; mean (SD)	400; 43.2 (25.99)	396; 42.7 (23.74)
Pre-bronchodilator FEV₁ mean (SD)	1,240.4 (482.04)	1,281.8 (537.00)
Pre-bronchodilator FVC mean (SD)	2,595.6 (827.49)	2,605.0 (782.47)

Source: MATINEE CSR (21); Sciurba 2025 (22); Data on File (pooled mITT-300 analysis) (27)

[†]Classification based on post-bronchodilator FEV₁ at Screening, GOLD reports for COPD; [‡]Participants with CV comorbidity are defined as participants with any past or current medical condition under Cardiac Disorders;

[¶]Participants with other comorbidity are defined as participants with any past or current medical condition other than under Cardiac Disorders; [§]Based on refined ABE assessment tool (GOLD report for COPD 2023); Group E participants have ≥2 moderate exacerbations or ≥1 exacerbation leading to hospitalisation; ^{††}SGRQ-C Total Score range 0-100 with higher scores indicating poor health-related quality of life; ^{‡‡}CAT score range 0-40 with higher scores indicating greater COPD disease impact; ^{¶¶}Number of exacerbations reported in the 12 months prior to study. In MATINEE, moderate exacerbations were treated with systemic corticosteroids, with or without antibiotics.

However, in studies METREO and METREX moderate exacerbations were treated with systemic corticosteroids and/or antibiotics; ^{§§}Information summarised for current and former smokers only in METREO. Smoking Pack Years=(Number of cigarettes smoked per day/20) x number of years smoked.

Abbreviations: BMI, body mass index; CAT, COPD assessment test; COPD, chronic obstructive pulmonary disorder; CSR, clinical study report; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; GERD, Gastroesophageal Reflux Disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mepo, mepolizumab; mITT, modified intention-to-treat; mMRC, modified medical research council score; PBO, placebo; SD, standard deviation; SGRQ-C, St. George's Respiratory Questionnaire – COPD specific.

2.3.2.2 METREX and METREO

Detailed baseline characteristics of the individual METREO mITT and METREX mITT trials (including the pre-specified pooled eosinophilic population) are provided in Appendix J.

The mITT-300 subgroups from these two trials are described in the pooled mITT-300 analysis section (Section 2.3.2.3).

2.3.2.3 Pooled mITT-300 population (MATINEE mITT, METREO mITT-300 and METREX mITT-300)

Baseline characteristics in the pooled mITT-300 population (Table 9) (27), were closely aligned with those observed in MATINEE (Table 8), supporting the clinical comparability of the datasets.

The mean age was 65.9 years, with over half (59%) of participants aged ≥65 years, similar to the

Company evidence submission for mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237]

61% in MATINEE. The population was predominantly male (67%) and White (83%), with a mean BMI of 27.03 kg/m², comparable to MATINEE (Table 8).

The mean duration of COPD ranged from 9.6 years, consistent with MATINEE (10.2 years in the mepolizumab group) (21, 22). The mean number of moderate/severe exacerbations in the 12 months prior to screening was 2.4 (SD 1.13), consistent with MATINEE values (2.3 mepolizumab vs. 2.2 placebo), reflecting a population with high exacerbation burden despite triple therapy. The impact on HRQoL was similar, with a pooled mean SGRQ-C score of 54.4 (17.51), indicative of a substantial symptom burden, consistent with the MATINEE trial population.

The mITT-300 populations of the METREO and METREX trials each demonstrated demographic and clinical profiles broadly consistent with MATINEE, including age distribution, sex ratio, COPD duration, exacerbation history, and HRQoL measures. Minor differences were observed such as the inclusion of a very small proportion of never smokers in the mITT-300 populations of the METREO and METREX trials (<1%) which were not permitted in MATINEE, and slightly lower BMI in METREO mITT-300. However, cumulative smoking exposure, lung function severity, and comorbidity patterns were comparable across all datasets.

Taken together, the pooled mITT-300 population is a clinically comparable group across trials, with demographic and disease characteristics well aligned to those in MATINEE, and representative of the patients for whom mepolizumab is intended in routine clinical practice.

Table 9: Pooled mITT-300 population (MATINEE mITT + METREO mITT-300 + METREX mITT-300): Participant baseline characteristics

	MATINEE		METREO mITT-300		METREX mITT-300		Pooled mITT-300		
	Mepo (N=403)	PBO (N=401)	Mepo (N=83)	PBO (N=87)	Mepo (N=82)	PBO (N=90)	Mepo (N=568)	PBO (N=578)	Total (N=1,146)
Age years, mean (SD)	66.4 (8.10)	66.0 (7.91)	65.2 (9.28)	65.8 (8.58)	65.5 (8.38)	64.4 (9.24)	65.7 (8.24)	66.1 (8.32)	65.9 (8.258)
Age group years, n (%)									
<40	1 (<1)	0	0	0	0	0	1 (<1)	0	1 (<1)
40 to <65	142 (35)	173 (43)	34 (41)	41 (47)	38 (46)	42 (47)	214 (38)	256 (44)	470 (41)
≥65	260 (65)	228 (57)	49 (59%)	46 (53%)	44 (54%)	48 (53%)	353 (62)	322 (56)	675 (59)
Sex, n (%)									
Female	127 (32)	126 (31)	33 (40)	28 (32)	29 (35)	33 (37)	189 (33)	187 (32)	376 (33)
Male	276 (68)	276 (68)	50 (60)	59 (68)	53 (65)	57 (63)	379 (67)	391 (68)	770 (67)
Race, n (%)									
American Indian/Alaskan Native	3 (<1)	2 (<1)	0	0	9 (11%)	5 (6)	12 (2)	7 (1)	19 (2)
Asian	56 (14)	56 (14)	17 (20)	18 (21)	0	1 (1)	73 (13)	75 (13)	148 (13)
Black or African American	5 (1)	5 (1)	1 (1)	1 (1)	2 (2)	2 (2)	8 (1)	8 (1)	16 (1)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0
White	338 (84)	335 (84)	65 (78%)	68 (78%)	68 (83%)	74 (82%)	471 (83)	477 (83)	948 (83)
Mixed Race	1 (<1)	3 (<1)	0	0	3 (4%)	8 (9%)	4 (<1)	11 (2)	15 (1)
Mean (SD) BMI, kg/m²	27.38 (5.342)	27.13 (5.540)	25.19 (3.98)	26.40 (4.56)	27.58 (5.49)	26.83 (5.19)	27.16 (5.340)	26.91 (5.370)	27.03 (5.354)
Mean (SD) duration of COPD, years	10.2 (6.65)	9.7 (5.88)	9.3 (6.58)	8.8 (10.0)	9.4 (5.90)	9.2 (7.06)	9.9 (6.79)	9.4 (5.90)	9.6 (6.36)

	MATINEE		METREO mITT-300		METREX mITT-300		Pooled mITT-300		
	Mepo (N=403)	PBO (N=401)	Mepo (N=83)	PBO (N=87)	Mepo (N=82)	PBO (N=90)	Mepo (N=568)	PBO (N=578)	Total (N=1,146)
Severity of airflow limitation[†], n (%)									
Mild ≥80% predicted	2 (<1)	3 (<1)	2 (2)	1 (1)	1 (1)	2 (2)	5 (<1)	6 (1)	11 (<1)
Moderate: ≥50% <80% predicted	168 (42)	181 (45)	40 (48)	31 (36)	30 (37)	33 (37)	238 (42)	245 (42)	483 (42)
Severe: ≥30% <50% predicted	180 (45)	160 (40)	31 (37)	40 (46)	45 (55)	48 (53)	256 (45)	248 (43)	504 (44)
Very severe: <30%	53 (13)	57 (14)	10 (12)	15 (17)	6 (7)	7 (8)	69 (12)	79 (14)	148 (13)
CV comorbidity[‡], n (%)	103 (26)	97 (24)	22 (27)	24 (28)	17 (21)	20 (22)	142 (25)	141 (24)	283 (25)
mMRC score at screening, n (%)									
mMRC <2	89 (22)	98 (24)	11 (13)	9 (10)	12 (15)	22 (24)	112 (20)	129 (22)	241 (21)
mMRC ≥2	310 (77)	301 (75)	72 (87)	78 (90)	70 (85)	68 (76)	452 (80)	447 (77)	899 (78)
Missing	4 (<1)	2 (<1)	0	0	0	0	4 (<1)	2 (<1)	6 (<1)
GOLD Group E[§], n (%)	401 (>99)	393 (98)	83 (100)	87 (100)	82 (100)	90 (100)	566 (>99)	570 (99)	1136 (>99)
Screening blood eosinophils, GI/L geometric mean (SD logs)	0.48 (0.378)	0.48 (0.398)	0.48 (0.392)	0.48 (0.397)	0.42 (0.287)	0.50 (0.481)	0.47 (0.370)	0.48 (0.411)	0.48 (0.392)
CAT total score^{††}, n; mean (SD)	389; 19.2 (6.95)	393; 19.1 (6.75)	80; 19.4 (7.42)	86; 19.3 (7.39)	78; 18.8 (7.90)	85; 19.4 (8.10)	547; 19.2 (7.15)	564; 19.2 (7.06)	1,111; 19.2 (7.10)
SGRQ-C total score^{††}, n; mean (SD)	388; 55.3 (17.73)	392; 53.9 (17.86)	82; 53.4 (16.69)	87; 53.6 (17.10)	79; 54.3 (17.54)	88; 55.1 (16.27)	549; 54.9 (17.53)	567; 54.0 (17.49)	1,116; 54.4 (17.51)
Number of moderate/severe exacerbations^{†††}, mean (SD)	2.3 (0.98)	2.2 (0.90)	2.8 (1.67)	2.6 (1.34)	2.6 (1.38)	2.6 (1.39)	2.4 (1.18)	2.3 (1.08)	2.4 (1.13)
Smoking history, n (%)									
Never smoker	0	0	0	1 (1)	1 (1)	7 (8)	1 (<1)	8 (1)	9 (<1)

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	MATINEE		METREO mITT-300		METREX mITT-300		Pooled mITT-300		
	Mepo (N=403)	PBO (N=401)	Mepo (N=83)	PBO (N=87)	Mepo (N=82)	PBO (N=90)	Mepo (N=568)	PBO (N=578)	Total (N=1,146)
Current smoker	111 (28)	111 (28)	22 (27)	23 (26)	27 (33)	28 (31)	160 (28)	162 (28)	322 (28)
Former smoker	292 (72)	290 (72)	61 (73)	63 (72)	54 (66)	55 (61)	407 (72)	408 (71)	815 (71)
Smoking pack years^{§§}, n; mean (SD)	400; 43.2 (25.99)	396; 42.7 (23.74)	83; 42.8 (29.86)	86; 43.4 (28.34)	81; 46.8 (29.55)	83; 43.0 (28.99)	564; 43.7 (27.10)	565; 42.8 (25.26)	1,129; 43.3 (26.18)

Source: MATINEE CSR (21); Sciurba 2025 (22); Data on File (pooled mITT-300 analysis) (27)

†Classification based on post-bronchodilator FEV₁ at Screening, GOLD reports for COPD; ‡Participants with CV comorbidity are defined as participants with any past or current medical condition under Cardiac Disorders; ¶Participants with other comorbidity are defined as participants with any past or current medical condition other than under Cardiac Disorders; §Based on refined ABE assessment tool (GOLD reports for COPD 2023); Group E participants have ≥2 moderate exacerbations or ≥1 exacerbation leading to hospitalisation; ††SGRQ-C Total Score range 0-100 with higher scores indicating poor health-related quality of life; ‡‡CAT score range 0-40 with higher scores indicating greater COPD disease impact; ¶¶¶Number of exacerbations reported in the 12 months prior to study. In MATINEE, moderate exacerbations were treated with systemic corticosteroids, with or without antibiotics. However, in studies METREO and METREX moderate exacerbations were treated with systemic corticosteroids and/or antibiotics; §§Information summarised for current and former smokers only in METREO. Smoking Pack Years=(Number of cigarettes smoked per day/20) x number of years smoked; †††Data points not reported. Baseline pre-bronchodilator FEV₁ and FVC were similar across the groups.

Abbreviations: BMI, body mass index; CAT, COPD assessment test; CSR, clinical study report; COPD, chronic obstructive pulmonary disorder; CV, cardiovascular; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA, long-acting beta₂-agonist; LAMA, long-acting muscarinic antagonist; mepo, mepolizumab; mITT, modified intention-to-treat; mITT-300, modified intention-to-treat 300 (participants with BEC ≥300 cells/μL at screening who received ≥1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline); mMRC, modified medical research council score; PBO, placebo; SD, standard deviation; SGRQ-C, St. George's Respiratory Questionnaire – COPD specific.

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

2.4.1 MATINEE

2.4.1.1 Analysis sets

A summary of the analysis sets in the MATINEE trial (21, 22) relevant to the data presented in this submission are provided in Table 10.

Table 10: Definition of analysis populations in the MATINEE trial

Analysis populations	Definition	Mepo SC N=404 n (%)	PBO N=402 n (%)	Total N=806 n (%)
mITT	All randomised patients who received at least one dose of trial medication. Patients were analysed by randomised treatment	403 (>99)	401 (>99)	804 (>99)
Safety population	All randomised patients who received at least one dose of trial medication. Patients were analysed based on actual treatment received for more than 50% of treatment administrations	403 (>99)	401 (>99)	804 (>99)

Source: MATINEE CSR (21)

Abbreviations: CSR, clinical study report; mepo, mepolizumab; mITT, modified intent-to-treat population; PBO, placebo.

2.4.1.2 Summary of statistical analyses

The MATINEE (21, 22) trial was designed to test the superiority of mepolizumab vs. placebo. The treatment comparison of interest for the primary and secondary endpoints was mepolizumab vs. placebo in the mITT population; the significance test was considered statistically significant at the two-sided 5% alpha level (one-sided 2.5%).

A hierarchical testing procedure was used to provide strong control of Type I error for multiplicity arising from the primary and multiple secondary endpoints (21, 22). This was carried out using a step-down closed testing procedure where inference for an endpoint in the pre-defined hierarchy was dependent on statistical significance having been achieved for the previous endpoints in the hierarchy.

For example, for the primary endpoint, mepolizumab was compared to placebo at a two-sided $\alpha=0.05$ (one-sided $\alpha=0.025$) (21, 22). The next endpoint in the hierarchy (i.e. the first secondary endpoint) was tested only if the test for the primary endpoint was significant at the one-sided 2.5% level (21, 22). Testing continued down the hierarchy for the remaining endpoints in an equivalent

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manner only if the previous endpoint in the hierarchy achieved statistical significance (21, 22). Endpoints tested outside of the statistical hierarchy are not controlled for multiplicity, and where $p < 0.05$, the result is considered nominally significant (21, 22).

The hierarchy of the primary and secondary endpoints tested was as follows (21, 22):

- Annualised rate of moderate/severe exacerbations (primary endpoint)
- Time to first moderate/severe exacerbation
- Proportion CAT score responders at Week 52
- Proportion of SGRQ total score responders at Week 52
- Proportion of Evaluating Respiratory Symptoms in COPD (E-RS:COPD) responders at Week 52
- Annualised rate of exacerbations requiring ED and/or hospitalisation.

A summary of the statistical analyses undertaken in the trials is provided in Table 11.

Table 11: Summary of statistical analyses in MATINEE

Statistical analysis of primary endpoint	The primary analysis of the rate of moderate/severe exacerbations was assessed with the use of a negative binomial model that included exacerbations that occurred during or after the treatment period with covariates of smoking status, number of exacerbations in the previous year, baseline severity of airflow obstruction, and geographic region, with the natural log of time included as an offset variable.
Statistical analysis of secondary endpoints	Time to first moderate/severe exacerbation: • The primary measure of treatment effect was the HR • Analysis of this endpoint used a Cox proportional hazards model allowing for covariates of smoking status, number of exacerbations in previous year, baseline disease severity and geographic region Proportion of CAT score responders at Week 52: • The CAT score ranges from 0–40 units, higher scores indicate a greater effect of disease. Response is defined as a ≥ 2-unit reduction in CAT score from baseline • Analysis was performed on each imputed dataset using a logistic regression model adjusting for baseline CAT score, smoking status, and geographic region. Results of these analyses were combined using Rubin's rule Proportion of SGRQ total score responders at Week 52 • The SGRQ for COPD total score ranges from 0–100 points, and higher scores indicate a worse health status. Response is defined as a ≥ 4-point reduction in SGRQ total score from baseline. Same approach and analysis methods were used as for the CAT score responders E-RS:COPD responders at Weeks 49–52 • The E-RS:COPD ranges from 0–40 units, and higher scores indicate more severe disease. Response is defined as a ≥ 2-unit reduction in E-RS:COPD from baseline. Same approach and analysis methods were used as for the CAT score responders

Statistical analysis of primary endpoint	The primary analysis of the rate of moderate/severe exacerbations was assessed with the use of a negative binomial model that included exacerbations that occurred during or after the treatment period with covariates of smoking status, number of exacerbations in the previous year, baseline severity of airflow obstruction, and geographic region, with the natural log of time included as an offset variable.
	Exacerbations resulting in ED visit and/or hospitalisation • Same methods of analysis as for the primary endpoint.
Statistical analysis of safety endpoints	All SAEs and potential MACE (CV death, non-fatal MI, non-fatal stroke) were subjected to blinded independent adjudication.
Statistical analysis of subgroups	For the primary endpoint, a separate exploratory analysis within each of the subgroup categories in Table 6 was carried out. Unless otherwise specified no formal hypothesis testing in subgroups of the population was performed, exacerbation rates/year in each treatment arm together with the RR and associated 95% CI was displayed. For secondary endpoints, exploratory analyses by subgroup categories in Table 6 was carried out. No formal hypothesis testing in subgroups of the population was performed. Bayesian hierarchical modelling was used to estimate subgroup-specific treatment effects for all subgroups (except eosinophil categories) by pooling information across subgroups. RRs from standard analyses were incorporated into the model, and shrinkage estimates with 95% credible intervals were generated. Sensitivity analyses explored the impact of prior assumptions on between-subgroup variability.
Sample size and power calculation	With an assumed true exacerbation rate of 1.7 exacerbations per year in the placebo arm and an anticipated 5.5% of patient years' data missing due to early trial withdrawals, it was approximated that 800 patients (400 per arm) would provide 90% power to detect a true 23% reduction in the annualised rate of moderate/severe exacerbations with mepolizumab at a two-sided 5% level of significance. Blinded re-evaluations of sample size were planned based on observed overall blinded exacerbation rates to assess the need for potential increases to maintain study power.
Randomisation	All patients were centrally randomised using an IWRS. The randomisation schedule was generated by PPD (ThermoFisher Scientific, USA) using validated randomisation SAS Software Version 9.4 (Proc Plan) and a fixed block size of four.
Data management and patient withdrawal	Patients with missing values owing to withdrawal from the trial were considered to have had no response.

Source: Sciurba 2025 (22), MATINEE CSR (21).

Abbreviations: CAT, COPD Assessment Test; CI, confidence interval; COPD, chronic obstructive pulmonary disorder; CSR, clinical study report; ED, emergency department; CV, cardiovascular; E-RS, evaluation of respiratory symptoms; HR, hazard ratio; IWRS, Interactive Web Response System; MACE, major adverse cardiac event; MI, myocardial infarction; mITT, modified intention to treat; RR, rate ratio; SAE, serious adverse event; SGRQ, St George's Respiratory Questionnaire.

2.4.1.3 Participant flow

The participant flow for MATINEE is provided in Appendix B.

2.4.2 METREX and METREO

Detailed statistical methods for the METREO (23, 25) and METREX (23, 24) trials (mITT and pre-specified pooled eosinophilic population [≥ 150 cells/ μL at screening or ≥ 300 cells/ μL in the prior 12 months]) are provided in Appendix J (Section J.2 and Section J.3).

2.4.2.1 Participant flow

The participant flow in the METREO and METREX trials is provided in Appendix B.

2.4.3 Pooled mITT-300 analysis (MATINEE [mITT], METREX [mITT-300] and METREO [mITT-300])

2.4.3.1 Analysis sets

The pooled analysis of efficacy data from the three trials includes all randomised participants who received ≥ 1 dose of study treatment in the MATINEE trial (21, 22), and participants from METREO and METREX with a screening BEC ≥ 300 cells/ μL who also received ≥ 1 dose of treatment. Together this analysis population is referred to as the pooled mITT-300 population(27).

2.4.3.2 Summary of statistical methods

The pooled analyses for the efficacy data comparisons were carried out for the endpoints shown in Table 12 using appropriate statistical models.

Data were summarised using appropriate measures (means/geometric means, SD, medians and ranges for continuous variables and frequencies and percentages in each category for categorical variables). For untransformed data, change from baseline at each time point is expressed as a difference (value at time point – value at baseline). For log_e transformed data, change from baseline at each time point was expressed as a ratio (value at time point/value at baseline). Estimates of treatment effect with corresponding 95% CI and p-value were presented.

Table 12: Endpoints for pooled analysis of data from MATINEE mITT, METREX mITT-300, and METREO mITT-300 (pooled mITT-300 population)

Category	Endpoint	Endpoint type in MATINEE
Exacerbations	Annualised rate of moderate/severe exacerbations	Primary
	Time to first moderate/severe exacerbation	Secondary
	Annualised rate of exacerbations requiring ED visit and/or hospitalisation	Secondary
	Time to first exacerbation requiring ED visit and/or hospitalisation	Other
	Annualised rate of severe exacerbations	Other

Category	Endpoint	Endpoint type in MATINEE
	Time to first severe exacerbation	Other
Symptoms	Proportion of CAT total score responders (≥ 2 unit reduction from baseline) at Week 52	Secondary
	Mean change from baseline in CAT total score at Week 52	Other
QoL	Proportion of SGRQ-C total score responders (≥ 4 point reduction from baseline) at Week 52	Secondary
	Mean change from baseline in SGRQ-C total score at Week 52	Other
eDiary	Occurrences of rescue medication use (occasions per day) during Weeks 49–52	Other
	Percentage of nights with no awakenings during Weeks 49–52	Other
Lung function	Mean change from baseline in pre-bronchodilator FEV ₁ at Week 52	Other
	Mean change from baseline in pre-bronchodilator FVC at Week 52	Other
Blood eosinophils	Ratio to baseline in blood eosinophils at Week 52	Other
Health outcomes	Clinician-rated response to therapy at Week 52	Other
	Participant-rated response to therapy at Week 52	Other

Source: MATINEE CSR (21); Sciurba 2025 (22).

Abbreviations: CAT, COPD assessment test; CSR, clinical study report; ED, emergency department; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; mITT, modified intention-to-treat; mITT-300 modified intention-to-treat 300 (participants with BEC ≥ 300 cells/ μ L at screening who received ≥ 1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline); QoL, quality of life; SGRQ-C, St. George's Respiratory Questionnaire – COPD specific.

Table 13: Summary of statistical analyses in the pooled mITT-300 population

Statistical analysis of primary endpoint	Annualised rate of moderate/severe exacerbations. Moderate exacerbations required systemic corticosteroids and/or antibiotics; severe exacerbations required hospitalisation (≥ 24 hours) or resulted in death. Events within 7 days were counted as a single exacerbation (highest severity). All events from treatment start to study withdrawal/completion were included. Analysis used a negative binomial model with covariates and an offset for time on and off treatment. The primary estimand excluded COVID-19–related intercurrent events (relevant to MATINEE only).
Statistical analysis of secondary endpoints	- Time-to-event endpoints (e.g. time to first moderate/severe exacerbation, ED/hospitalisation, and first severe exacerbation) were analysed using Cox proportional hazards models. - Annualised rates of ED/hospitalisation and severe exacerbations were analysed using negative binomial models. - CAT and SGRQ-C responder rates were assessed using logistic regression; mean change from baseline was analysed using MMRM.
Covariates	The following covariates were included in the statistical analysis models for all exacerbation-related endpoints: Smoking status (current vs. never/former)

Statistical analysis of primary endpoint	Annualised rate of moderate/severe exacerbations. Moderate exacerbations required systemic corticosteroids and/or antibiotics; severe exacerbations required hospitalisation (≥ 24 hours) or resulted in death. Events within 7 days were counted as a single exacerbation (highest severity). All events from treatment start to study withdrawal/completion were included. Analysis used a negative binomial model with covariates and an offset for time on and off treatment. The primary estimand excluded COVID-19–related intercurrent events (relevant to MATINEE only).
	• Number of moderate/severe exacerbations in previous year (≤ 2, 3, ≥ 4 as an ordinal variable) • Baseline disease severity (as % predicted post-bronchodilator FEV₁) • Geographic region (US, EU, Rest of World) • Study (MATINEE, METREO, METREX) Participants with missing covariate information were excluded from the analysis.
Subgroups of interest	Analysis of the following subgroups were carried out based on data from studies MATINEE, METREO, and METREX: • Screening BEC threshold: <500; ≥ 500 cells/μL • Age: <40; 40–<65; ≥ 65 years • Sex: Male; Female • Race: African American/African Heritage; White; Asian; Other • Geographic region: EU; US; Rest of World • Exacerbations in the previous year: ≤ 2; 3; ≥ 4 exacerbations • Smoking status at screening: Current; Never; Former • Severity of airflow limitation (GOLD Reports): Mild; Moderate; Severe; Very Severe • Symptoms of chronic bronchitis: Yes[†]; No • Chronic bronchitis symptoms + screening BEC: Yes[†] + ≥ 500; Yes[†] + <500; No + ≥ 500; No + <500
Sample size and power calculation	The p-values presented are not adjusted for multiplicity unless specified otherwise. Adjustments for multiple treatment comparisons were made within each of the individual studies and are described within the study protocols and SAPs. Statistical testing for superiority was conducted for the individual studies; the hierarchical order of testing the primary and secondary endpoints is described for each study in Appendix J
Health outcomes	Participant and clinician rated response to therapy are summarised for the combined studies regardless of treatment discontinuation or occurrence of any other intercurrent events.

Source: Data on File (m2.7.3 Summary of Clinical Efficacy) (27)

[†]Symptoms of chronic bronchitis=Y, refers to participants with baseline response of “most days of the week” or “several days of the week” to both questions regarding cough and sputum on SGRQ-C questionnaire.

Abbreviations: BEC, blood eosinophil count; CAT, COPD assessment test; COPD, chronic obstructive pulmonary disorder; COVID-19, coronavirus disease 2019; ED, emergency department; EU, Europe; FEV₁, forced expiratory volume in one second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mITT-300 modified intention-to-treat 300 (participants with BEC ≥ 300 cells/ μ L at screening who received ≥ 1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline); MMRM, mixed model for repeated measures; SGRQ, St. George’s Respiratory Questionnaire – COPD specific; US, United States.

2.4.3.3 Participant flow

Detailed information on the derivation of the analysis population for the pooled mITT-300 population analysis is presented in Appendix B.

2.5 Critical appraisal of the relevant clinical effectiveness evidence

Quality assessment of mepolizumab trials was conducted using the methods described in the Cochrane Handbook (188). A summary of the risk of bias assessment is provided in Table 14. The full details of which are provided in Appendix B.

Table 14: Risk of bias assessment

Bias domain	MATINEE (21, 22)	METREX (23, 24)	METREO (23, 25)
Random sequence generation	Low	Low	
Allocation concealment	Low	Low	
Blinding of participants and personnel	Low	Low	
Blinding of outcome assessment	Unclear	Unclear	
Incomplete outcome data	Low	Low	
Selective reporting	Low	Low	
Other source of bias	Low	Low	
Testing decisions	Unclear	Unclear	
Treatment decisions	Unclear	Unclear	

The core evidence supporting the clinical effectiveness of mepolizumab is drawn from a pooled analysis of the pooled mITT-300 population (all participants from MATINEE (21, 22) and participants from METREX (23, 24), and METREO (23, 25) with BEC ≥ 300 cells/ μ L at screening). Although the pooled analysis was conducted post-hoc and therefore carries a potential risk of bias, the results were highly consistent with those observed in the individual trials, particularly MATINEE, which was prospectively designed. The strong internal validity of the studies and the consistency of treatment effects between the pooled analysis and the individual trial results reinforce the robustness and reliability of the pooled findings. As such, the use of a pooled analysis for all outcomes is considered appropriate and is consistent with both the individual trial results and the intended real-world use of mepolizumab in eosinophilic COPD.

2.5.1 Applicability of trial populations to clinical practice in England

MATINEE (21, 22), METREX (23, 24), and METREO (23, 25) recruited patients globally, including 23 (3%) participants from three sites in the UK in MATINEE (21, 22), and eight (4%) participants from five sites in the UK in METREO (23, 25). There were no UK sites in the METREX (23, 24) trial.

Key demographic and disease characteristics in the trials (including age, gender distribution, GOLD stage at baseline, exacerbation history) were considered reflective of the population of patients with uncontrolled COPD of an eosinophilic phenotype despite treatment on a combination of an ICS + LABA + LAMA in England. Real-world data from patients with COPD across Europe indicate that approximately 6% of those on triple therapy have BEC ≥ 300 cells/ μ L and meet exacerbation criteria, closely matching the pooled mITT-300 population (189). This alignment underlines the relevance of the pooled mITT-300 population to a clinically important subgroup in routine care. Patients in the UK subset of Benson *et al.*, 2019 (189) who met the eosinophil and exacerbation criteria show very similar demographics, BMI, smoking status, and exacerbation history to the pooled mITT-300 trial population (27). The slightly lower mMRC score and higher mean FEV₁ in the UK real-world group likely reflect the broader clinical spectrum seen in routine care vs. the more selective inclusion criteria of clinical trials. Overall, the alignment in key baseline characteristics supports the applicability of the trial population to clinical practice in England.

In all trials, participants received consistent background SoC in the form of triple inhaled therapy (ICS + LABA + LAMA), in line with UK clinical practice as described in NICE guideline NG115 (19). This alignment in background therapy across studies further supports the comparability of the trial populations to each other and to routine clinical practice in England.

2.6 Clinical effectiveness results of the relevant studies

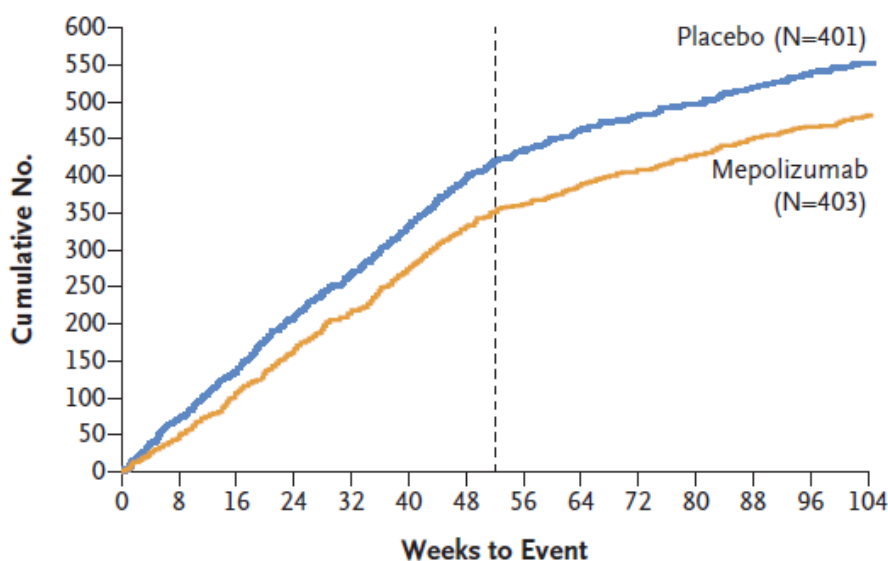
Efficacy results for the MATINEE trial (21, 22) are presented in Section 2.6.1, with a full set of detailed results for additional efficacy endpoints provided in Appendix J (Section J.1). Results for the mITT population of the METREO and METREX trials are provided in Appendix J (Section J.2). In Section 2.6.3, MATINEE outcomes are discussed alongside the mITT-300 populations from METREO and METREX (27) as part of the pooled mITT-300 analysis, comparing results across studies to highlight similarities and differences. The pooled mITT-300 efficacy results from all three trials are presented as supportive evidence for MATINEE.

2.6.1 MATINEE

2.6.1.1 Primary endpoint: Annualised rate of moderate/severe exacerbations up to Week 104

Treatment with mepolizumab resulted in a statistically significant reduction in the annualised rate of moderate/severe exacerbations compared with placebo (rate ratio [RR] 0.79; 95% CI: 0.66, 0.94; $p=0.011$; Table 15). Over the follow-up period, fewer patients treated with mepolizumab compared with placebo experienced one or more moderate/severe exacerbations (50% vs. 56%, respectively) (21, 22). As shown in Figure 8, the cumulative incidence curves separated early and remained consistently apart through Week 104, indicating an early and sustained reduction in the risk of moderate/severe exacerbations with mepolizumab over the 2 years of follow-up.

Figure 8: Cumulative number of moderate or severe exacerbations



Source: Sciurba 2025 (22).

Table 15: MATINEE: Primary endpoint – Annualised frequency of moderate/severe exacerbations (Week 104 mITT population)

	Mepo (N = 403)	PBO (N = 401)
Exacerbation rate/year	0.80 (0.70, 0.91)	1.01 (0.89, 1.15)
RR (mepolizumab/placebo) (95% CI)	0.79 (0.66, 0.94); $p=0.011$	

Source: MATINEE CSR (21), Table 22; Sciurba 2025 (22)

Abbreviations: CI, confidence interval, CSR, clinical study report; mepo, mepolizumab; mITT, modified intention to treat; PBO, placebo; RR, rate ratio.

2.6.1.2 Key secondary endpoints

2.6.1.2.1 Time to first moderate/severe exacerbation

The Kaplan–Meier (KM) median time to the first moderate or severe exacerbation was 419 days (95% CI: 332, 530) in the mepolizumab group and 321 days (95% CI: 262, 396) in the placebo group, with a 23% lower hazard of a moderate or severe exacerbation through Week 104 in the mepolizumab group than in the placebo group (HR 0.77 [95% CI: 0.64, 0.93; p=0.009) (Figure 9, Table 16). At Week 52, 172 patients in the mepolizumab group and 146 patients in the placebo group remained free of a first moderate or severe exacerbation, indicating that more patients receiving mepolizumab avoided such events over the first year of treatment (Figure 9).

Table 16: MATINEE: Secondary endpoint – Time to first moderate or severe exacerbation (Week 104 mITT population)

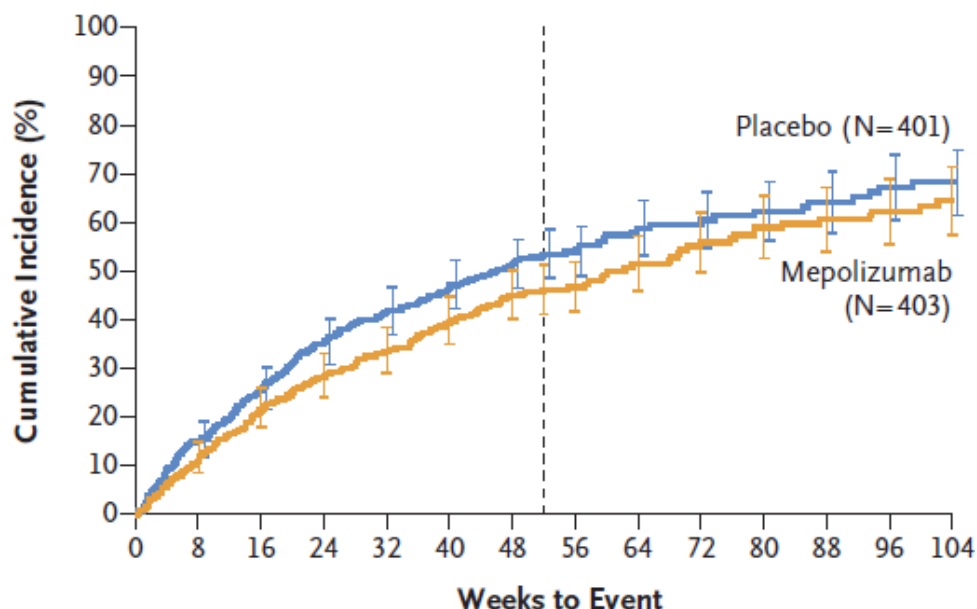
	Mepo (N = 403)	PBO (N = 401)
By Week 104†		
Participants with events	██████	██████
Probability (%) of an exacerbation (95% CI)	64.5 (57.5, 71.4)	68.3 (61.4, 74.9)
KM median time to first moderate or severe exacerbation up to Week 104 vs. PBO (95% CI) days	419 (332, 530)	321 (262, 396)
Event: first moderate/severe exacerbation, n (%)	██████	██████
Censored, n (%)	██████	██████
Censored at study withdrawal	██████	██████
Censored at study completion	██████	██████
Censored due to COVID-19 pandemic related ICE	██████	██████
HR (mepo/PBO) (95% CI); p value	0.77 (0.64, 0.93); p=0.009	

Source: MATINEE CSR (21), Table 22; Sciurba 2025 (22).

†One participant had their first exacerbation on Day 733 which was included in the analysis model, however since the event occurred after Day 728, this event has not been counted in the “By Week 104” category.

Abbreviations: CI, confidence interval, COVID-19, coronavirus disease 2019; CSR, clinical study report; HR, hazard ratio; ICE, intercurrent event; KM, Kaplan–Meier; PBO, placebo; mepo, mepolizumab; mITT, modified intention to treat.

Figure 9: Cumulative incidence of first moderate or severe exacerbation (mITT)



No. at Risk

Placebo	401	333	292	250	223	203	180	71	56	46	41	37	32	22
Mepolizumab	403	355	309	277	251	222	202	82	69	58	52	48	41	24

Source: Sciurba 2025 (22).

The initial fixed trial duration of 52 weeks (dashed lines) was extended to a variable duration of up to 104 weeks after the receipt of regulatory approval. Bars indicate 95% confidence intervals, which have not been adjusted for multiplicity and should not be used for inference about treatment effects.

Abbreviations: mITT, modified intention-to-treat.

2.6.1.2.2 COPD Assessment Test

A response as assessed with the CAT, defined as a decrease of at least two points in the CAT score from baseline to Week 52, occurred in 41% of the patients in the mepolizumab group and in 46% of those in the placebo group (odds ratio [OR] 0.81 [95% CI: 0.60, 1.09] (Table 17).

Table 17: MATINEE: Secondary endpoint – CAT score responders (Week 52 mITT population)

Response defined as a decrease in the CAT score ^{†,‡}	Mepo (N = 403)	PBO (N = 401)
Week 52, n	391	394
Responder n (%)	162 (41)	180 (46)
Non-responder n (%)	220 (56)	206 (52)
No change/worsening n (%)	██████	██████
Withdrawal from study prior to visit n (%)	██████	██████
Missing visit	██████	██████
Imputed, n (%)	██████	██████
OR mepo vs. PBO (95% CI); p value	0.81 (0.60, 1.09); p=0.161	

Response defined as a decrease in the CAT score ^{†,‡}	Mepo (N = 403)	PBO (N = 401)
Relative risk of response mepolizumab vs. PBO (95% CI) [¶]	0.92 (0.81, 1.05)	

Source: MATINEE CSR (21), Table 22 and Table 36; Sciurba 2025 (22)

†A response was defined as a decrease of at least 2 points in the CAT score from baseline to Week 52; ‡The difference between the trial groups was not significant. Therefore, the remaining end points in the hierarchical testing strategy were not assessed; ¶The relative risk was calculated in a post hoc analysis.

Abbreviations: CAT, COPD assessment test; CI, confidence interval, CSR, clinical study report; COPD, chronic obstructive pulmonary disorder; mepo, mepolizumab; mITT, modified intention-to-treat; PBO, placebo; RR, relative risk.

2.6.1.2.3 St. George's Respiratory Questionnaire

A response as defined by a decrease of at least four points in the SGRQ total score from baseline to Week 52 occurred in 50% of the patients in the mepolizumab group and in 46% of those in the placebo group (OR 1.17 [95% CI: 0.87, 1.57] (Table 18).

Table 18: MATINEE: Secondary endpoint – SGRQ total score responders (Week 52 mITT population)

Response, defined as a decrease in the SGRQ total score [†]	Mepo (N = 403)	PBO (N = 401)
Week 52, n	390	393
Responder n (%)	195 (50)	179 (46)
Non-responder n (%)	186 (48)	206 (52)
No change/worsening n (%)		
Withdrawal from study prior to visit n (%)		
Missing visit		
Imputed, n (%)		
OR vs. placebo (95% CI); p value	1.17 (0.87, 1.57); p=0.291	
Relative risk of response mepo SC vs. placebo (95% CI) [‡]	1.04 (0.91, 1.20)	

Source: MATINEE CSR (21), Table 22 and Table 38; Sciurba 2025 (22)

†A response was defined as a decrease of at least 4 points in the SGRQ total score from baseline to Week 52; ‡The relative risk was calculated in a post hoc analysis

Abbreviations: CI, confidence interval, CSR, clinical study report; mepo, mepolizumab; mITT, modified intention to treat; OR, odds ratio; PBO, placebo; SGRQ, St. George's Respiratory Questionnaire.

2.6.1.2.4 Evaluating Respiratory Symptoms (E-RS) in COPD

The percentage of patients with a response as defined by a decrease of at least two points in the E-RS:COPD total score from baseline to Weeks 49 through 52 was 31% in the mepolizumab group and 34% in the placebo group (OR 0.82 [95% CI: 0.60, 1.12]) (Table 19).

Table 19: MATINEE: Secondary endpoint – E-RS:COPD score responders (Week 52 mITT population)

Response defined as a decrease in the E-RS COPD score [†]	Mepo (N = 403)	PBO (N = 401)
Week 49–52, n	403	399
Responder n (%)	123 (31)	137 (34)
Non-responder n (%)	271 (67)	254 (64)
No change/worsening n (%)	██████	██████
Withdrawal from study prior to visit n (%)	██████	██████
Missing visit	██████	██████
Imputed, n (%)	██████	██████
Odds ratio mepo vs. PBO (95% CI); p value	0.82 (0.60, 1.12); p=0.209	
Relative risk of response vs. PBO (95% CI) [‡]	0.87 (0.72, 1.04)	

Source: MATINEE CSR (21), Table 22 and Table 41; Sciurba 2025 (22).

[†]A response was defined as a decrease of at least 2 points in the E-RS–COPD total score from baseline to weeks 49 through 52 (calculated as the mean of all the total scores during this period); [‡]The relative risk was calculated in a post hoc analysis

Abbreviations: CI, confidence interval, CSR, clinical study report; E-RS, evaluating respiratory symptoms; mITT, modified intention to treat; mepo, mepolizumab; PBO, placebo; SC, subcutaneous.

2.6.1.2.5 Exacerbations requiring ED visits/hospitalisations

The annualised rate of exacerbations leading to an ED visit, hospitalisation, or both was 0.13 events per year with mepolizumab and 0.20 events per year with placebo (RR 0.65 [95% CI: 0.43, 0.96] (Table 20).

Table 20: MATINEE: Secondary endpoint – annualised frequency of exacerbations requiring ED visit or hospitalisation (Week 104 mITT population)

	Mepo (N = 403)	PBO (N = 401)
Number of severe exacerbations requiring ED visit or hospitalisation[†], n (%)		
0	██████	██████
>0 <1	██████	██████
1 <2	██████	██████
2 <3	██████	██████
3 <4	██████	██████
4 <5	██████	██████
5 <6	██████	██████
6 <7	██████	██████
7 <8	██████	██████
8 <9	██████	██████
9 <10	██████	██████

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	Mepo (N = 403)	PBO (N = 401)
≥10	██████	██████
Annualised rate of exacerbations requiring ED visit and/or hospitalisation (95% CI)	0.13 (0.10, 0.18)	0.20 (0.15, 0.27)
Rate ratio (mepo/placebo) (95% CI)	0.65 (0.43, 0.96); p=0.032 [‡]	

Source: MATINEE CSR (21), Table 22 and Table 31; Sciurba 2025 (22).

†Nominal significance due to a break in the pre-defined statistical testing hierarchy; ‡Based on the crude annualised rate of exacerbations.

Abbreviations: CI, confidence interval, CSR, clinical study report; ED, emergency department; mepo, mepolizumab; mITT, modified intention to treat; PBO, placebo.

2.6.1.3 Additional efficacy and health outcomes endpoints

Among the additional efficacy and health outcomes endpoints from the MATINEE trial, statistical significance was observed only for the annualised rate by Week 104 of moderate/severe exacerbations requiring corticosteroids and antibiotics (mepolizumab: 0.40 [95% CI: 0.33, 0.47]; placebo: 0.53 [95% CI: 0.45, 0.62]; RR: 0.76 [95% CI: 0.60, 0.95]). A summary of the additional efficacy and health outcome endpoints measured in the MATINEE trial is provided in Table 21; for detailed results refer to Appendix J.

Table 21: Summary additional efficacy and health outcomes endpoints from the MATINEE trial (mITT population)

Outcome	Mepo (N = 403)	PBO (N = 401)	Treatment effect (mepo vs. PBO) (95% CI); p value
Additional efficacy endpoints			
Time to first exacerbation requiring ED visit and/or hospitalisation (Week 104), n (%)	██████	██████	██████
Annualised rate of severe exacerbations (on- and off-treatment; event/year) [†] (Week 104), n (%)	0.10 (0.07, 0.14)	0.15 (0.11, 0.21)	RR [‡] : 0.66 (0.43, 1.01); p=0.055
Proportion of participants with at least one severe exacerbation, n (%)	46 (11)	59 (15)	Rel Risk ^{††} : 0.78 (0.54, 1.11); p=0.166
Time to first severe exacerbation (Week 104), n (%)	██████	██████	██████
Annualised rate of moderate/severe exacerbations (95% CI), corticosteroids (Week 104)	██████	██████	██████
Annualised rate of moderate/severe exacerbations (95% CI), antibiotics alone (Week 104)	██████	██████	██████
Annualised rate of moderate/severe exacerbations (95% CI), treated with corticosteroids and antibiotics (Week 104)	██████	██████	██████

Outcome	Mepo (N = 403)	PBO (N = 401)	Treatment effect (mepo vs. PBO) (95% CI); p value
Change from baseline pre-bronchodilator FEV ₁ (mL) (Week 52), LS mean change (SE)	+24.6 (18.38)	+33.6 (18.38)	LS mean diff ^{§,†††} : -9.0 (-60.06, 42.06); p=0.730
Change from baseline pre-bronchodilator FVC (mL) (Week 52), LS mean change (SE)	██████	██████	LS mean diff ^{§,†††} : ██████
Health outcomes endpoints			
Change from baseline to Week 52 in EQ-5D- 3L index score, N; mean (SD)	██████ ██████	██████ ██████	-
HCRU to Week 104 ^{†††,††††} associated with COPD exacerbation:			
Patients with ≥1 exacerbation (any) ^{†††,††††} n (%)	204 (51)	227 (57)	=
Total number of exacerbations (any)	488	555	=
Number of days in general ward			
Exacerbations requiring resource ^{¶¶¶¶} n (%)	60 (12)	67 (12)	-
Total	396	419	-
Number of days in intensive care			
Exacerbations requiring resource ^{¶¶¶¶} n (%)	22 (5)	22 (4)	-
Total	85	124	-
Number of emergency room visits			
Exacerbations requiring resource ^{¶¶¶¶} n (%)	53 (11)	86 (15)	-

Source: MATINEE CSR (21); Sciurba 2025 (22); Criner 2025 (173).

Additional detail for additional efficacy endpoints and health outcome endpoints reported in the table are provided in detail in Appendix J.

†Estimated from a Cox proportional Hazards Model with covariates of treatment group, smoking status, baseline % predicted FEV₁, number of exacerbations in previous year (as an ordinal variable), and geographic region (as defined for the study/ISE); ‡Analysis performed using a negative binomial regression model with covariates of treatment group, smoking status, baseline % predicted FEV₁, number of exacerbations in previous year (as an ordinal variable), and geographic region (as defined for the study/ISE) with log(time in on- and off-treatment period) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions; ¶Contains both on-treatment and off-treatment exacerbation data. CMH adjusted relative risk to placebo; §Analysis performed using mixed model repeated measures with covariates of baseline score, geographic region (as defined for the study/ISE), smoking status (current vs. never/ ex-smoker) and treatment and visit, plus interaction terms for visit by baseline and visit by treatment group. Estimates are based on weighting applied to each level of class variable determined from observed proportions; †††Estimates are based on weighting applied to each level of class variable determined from observed proportions; ††††HCRU data were collected via patient recall at scheduled study visits using case report forms. There was no formal adjudication, source verification (e.g. medical record review), or standardised HCRU tool. Therefore, these data should be considered exploratory and interpreted with caution. †††††Defined as exacerbations requiring hospitalization ≥24 hours or resulting in death; ††††Includes exacerbations of any type (including moderate, severe, requiring ED visit etc); ¶¶¶¶Calculated using “total number of exacerbations (any)” as denominator; †††††Data collected from all patients regardless of length of enrolment
Abbreviations: CI, confidence interval; CSR, clinical study report; ED, emergency department; FEV₁, forced expiratory

volume in 1 second; FVC, forced vital capacity; HCRU, healthcare resource use; mepo, mepolizumab; LS, least squares; MAR, missing at random; mITT, modified intention-to-treat; PBO, placebo; Rel, relative; RR, rate ratio; SD, standard deviation; SE, standard error.

2.6.2 METREX and METREO

Detailed results of the individual METREO mITT and METREX mITT trials (including the pre-specified pooled eosinophilic population) are provided in Appendix J.

Results for the mITT-300 subgroups from these two trials are described in the pooled mITT-300 analysis section (Section 2.6.3).

2.6.3 Pooled analysis of data from MATINEE mITT, METREO mITT-300 and METREX mITT-300 (pooled mITT-300 population)

A total of 568 patients received mepolizumab and 578 patients received placebo were included in the pooled mITT-300 population.

2.6.3.1 Annualised rate of moderate/severe exacerbations

In MATINEE (21, 22), treatment with mepolizumab resulted in a statistically significant and clinically meaningful 21% reduction in the annualised rate of moderate/severe exacerbations compared with placebo group ($p=0.011$; Table 22: [the rationale for clinical significance is discussed further in Section 2.6.1.1]).

Over the treatment period, the cumulative number of exacerbations was fewer in the mepolizumab group than the placebo group. The treatment estimates in the METREO mITT-300 (27) and the METREX mITT-300 (27) populations were generally similar to MATINEE (Table 22:). Over the treatment period, the cumulative number of exacerbations was fewer in the mepolizumab group compared with the placebo group. In the pooled mITT-300 analysis (27), there was a 21% reduction in the annualised rate of moderate/severe exacerbations for mepolizumab compared with placebo (RR 0.79[‡] [95% CI 0.68, 0.91] $p=0.002$; Table 22:). Overall, these findings indicate a consistent treatment effect across the studies.

Table 22: Pooled mITT-300 population (MATINEE mITT + METREO mITT-300 + METREX mITT-300): Annualised rate of moderate/severe exacerbations

	MATINEE		METREO mITT-300		METREX mITT-300		Pooled mITT-300	
	Mepo	PBO	Mepo	PBO	Mepo	PBO	Mepo	PBO
N	403	401	■	■	■	■	568	578
Exacerbation rate/year	0.80	1.01	■	■	■	■	■	■

	MATINEE		METREO mITT-300		METREX mITT-300		Pooled mITT- 300	
	Mepo	PBO	Mepo	PBO	Mepo	PBO	Mepo	PBO
Rate ratio [†] (mepo/PBO) (95% CI)	0.79 [†] (0.66, 0.94); p=0.011		██████████		██████████		0.79 [†] (0.68, 0.91); p=0.002	

Source: MATINEE CSR (21); Sciurba 2025 (22); Data on File (pooled mITT-300 analysis) (27)

† Analysis performed using a negative binomial regression model with covariates of treatment group, smoking status, baseline % predicted FEV₁, number of exacerbations in previous year (as an ordinal variable), and geographic region (as defined for the study/ISE) with log(time in on- and off-treatment period) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions; ‡Analysis model as in footnote "†" with an additional covariate of study.

Abbreviations: CI, confidence interval, FEV₁, forced expiratory volume in one second; ICS, inhaled corticosteroid; LABA, long-acting beta₂-agonist; LAMA, long-acting muscarinic antagonist; mepo, mepolizumab; PBO, placebo; pooled mITT-300, modified intention-to-treat 300 (participants with BEC ≥300 cells/μL at screening who received ≥1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline).

2.6.3.2 Time to first moderate/severe exacerbation

In the MATINEE trial (21, 22), cumulative incidence, as seen in the KM plot, showed that the probability of a first moderate/severe exacerbation was lower for the mepolizumab group compared with the placebo group over the course of the study (Table 23). The time-to-first event analysis showed a statistically significant reduction in the risk of moderate/severe exacerbation for the mepolizumab group compared with the placebo group (HR 0.77 [95% CI: 0.64, 0.93]; p=0.009) (Table 23). Consistent results showing estimates of HR that favoured mepolizumab treatment were observed in the mITT-300 populations of the METREO and METREX trials (Table 23). The results from the pooled mITT-300 population (27) were consistent with MATINEE as seen in the KM plot (Appendix J); and the probability of having a moderate/severe exacerbation was lower in the mepolizumab group compared with the placebo group with a HR of █████ (95% CI: █████); p █████ (Table 23). Overall, these results, in combination with results for the primary endpoint, support a consistent impact on exacerbations for mepolizumab in the target population.

Table 23: Pooled mITT-300 population (MATINEE mITT + METREO mITT-300 + METREX mITT-300): Time to first moderate or severe exacerbation

	MATINEE		METREO mITT-300		METREX mITT-300		Pooled mITT-300	
	Mepo	PBO	Mepo	PBO	Mepo	PBO	Mepo	PBO
N	403	401	████	████	████	████	568	578
Week 52 probability (%) of an exacerbation [†] (95% CI)	46.1 (41.2, 51.2)	53.4 (48.5, 58.5)	████	████	████	████	████	████

	MATINEE		METREO mITT-300		METREX mITT-300		Pooled mITT-300	
	Mepo	PBO	Mepo	PBO	Mepo	PBO	Mepo	PBO
Week 104 probability (%) of an exacerbation [†] (95% CI)	64.5 (57.5, 71.4)	68.3 (61.4, 74.9)						
HR [‡] (mepo/PBO) (95% CI); p value	0.77 (0.64, 0.93); p=0.009							

Source: MATINEE CSR (21); Sciurba 2025 (22); Data on File (pooled mITT-300 analysis) (27)

[†]Kaplan-Meier estimate (MATINEE study to Week 104 [the initial fixed trial duration of 52 weeks (dashed lines) was extended to a variable duration of up to 104 weeks after the receipt of regulatory approval, protocol amendment] and METREX and METREO studies to Week 52); [‡]Estimated from a Cox proportional Hazards Model with covariates of treatment group, smoking status, baseline % predicted FEV₁, number of exacerbations in previous year (as an ordinal variable), and geographic region (as defined for the study/ISE). ¶Analysis model as in footnote “[‡]” with an additional covariate of study.

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; FEV₁, forced expiratory volume in one second; HR, hazard ratio; ICE, intercurrent event; ICS, inhaled corticosteroid; KM, Kaplan-Meier; LABA, long-acting beta₂-agonist; LAMA, long-acting muscarinic antagonist; mepo, mepolizumab; mITT-300, modified intention-to-treat 300 (participants with BEC ≥300 cells/μL at screening who received ≥1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline); NA, not applicable; PBO, placebo.

2.6.3.3 Exacerbations requiring ED visits/hospitalisations

Annualised rate of exacerbations requiring ED visit/hospitalisation: In the MATINEE trial (21, 22), participants treated with mepolizumab showed a 35% reduction in the annualised rate of exacerbations requiring ED visit/hospitalisation compared with placebo (RR: 0.65 [95% CI: 0.43, 0.96] p=0.032) (Table 24). Similar rate reduction as seen in the MATINEE trial was observed in the METREO mITT-300 population (27). A numerically lower reduction in rate of exacerbations requiring ED visit/hospitalisation was observed in the METREX mITT-300 population (27). In totality, for the pooled mITT-300 population (27), participants treated with mepolizumab showed a 29% reduction in annualised rate of exacerbations requiring ED visit and/or hospitalisation compared with placebo group (RR: 0.71 [95% CI: 0.51, 0.98 p=0.038]) (Table 24).

Time to first exacerbation requiring ED visit/hospitalisation: In the MATINEE trial (21, 22), cumulative incidence as seen in the KM plot (Appendix J) showed that the probability of a first moderate/severe exacerbation was lower for the mepolizumab group compared with the placebo group over the course of the study (Table 24). The time-to-first event analysis showed a reduction in the risk of exacerbation requiring ED visit and/or hospitalisation for mepolizumab compared with placebo (HR:  [95% CI: ] p=) (Table 24). Consistent results showing the HR favoured mepolizumab treatment over placebo were observed across the mITT-300 population from the METREO and METREX trials (Table 24) (27). The reduction in risk of an

exacerbation requiring ED visit/hospitalisation in the pooled mITT-300 population (27) was consistent with the reductions in moderate and severe exacerbations observed in MATINEE, METREO and METREX (Table 24).

Proportion of participants with at least one exacerbation requiring ED visit/hospitalisation:

In the MATINEE trial (21, 22), a lower proportion of participants had at least one exacerbation requiring ED visit/hospitalisation following mepolizumab (14%) treatment compared with placebo (18%). The risk of having ≥ 1 exacerbation requiring ED visit/hospitalisation was numerically lower for participants treated with mepolizumab compared with placebo (relative risk: 0.78 [95% CI: 0.57, 1.08] $p=0.139$) (Table 24). Consistent results showing the HR favoured mepolizumab treatment over placebo were observed across the mITT-300 population from the METREO and METREX trials (Table 24) (27). The risk of having at least one exacerbation requiring ED visit/hospitalisation in the pooled mITT-300 population (27) was numerically lower for participants treated with mepolizumab compared with placebo (relative risk: [REDACTED] [95% CI: [REDACTED]] $p=[REDACTED]$) (Table 24), was consistent with the risk reported in the MATINEE trial.

Table 24: Pooled mITT-300 population (MATINEE mITT + METREO mITT-300 + METREX mITT-300): Exacerbations requiring ED visit or hospitalisation

hospitalisation

	MATINEE		METREO mITT-300		METREX mITT-300		Pooled mITT-300	
	Mepo	PBO	Mepo	PBO	Mepo	PBO	Mepo	PBO
N	403	401	■	■	■	■	568	578
Rate of exacerbations requiring ED visit and/or hospitalisation								
Annualised rate of exacerbations requiring ED visit and/or hospitalisation (95% CI)	0.13 (0.10, 0.18)	0.20 (0.15, 0.27)	■	■	■	■	■	■
Rate ratio† (mepolizumab/PBO) (95% CI)	0.65 (0.43, 0.96); p=0.032		■		■		0.71‡ (0.51, 0.98); p=0.038	
Time to exacerbation requiring ED visit and/or hospitalisation								
Week 52 probability (%) exacerbation requiring ED visit /hospitalisation¶ (95% CI)	12.7 (9.8, 16.5)	16.2 (12.8, 20.3)	■	■	■	■	■	■
Week 104 probability (%) exacerbation requiring ED visit /hospitalisation¶ (95% CI)	17.6 (13.4, 23.0)	23.4 (18.2, 29.7)	■	■	■	■	■	■
HR§ (mepolizumab/PBO) (95% CI); p value	0.73 (0.51, 1.04); p=0.079		■		■		■	
Participants with ≥1 exacerbation requiring ED/hospitalisation								
Participants with ≥1 exacerbation requiring ED/hospitalisation## n (%)	56 (14)	71 (18)	■	■	■	■	■	■
Relative risk mepolizumab to PBO (95% CI); p value	0.78 (0.57, 1.08); p=0.139		■		■		■	

Source: MATINEE CSR (21); Sciurba 2025 (22); Data on File (pooled mITT-300 analysis) (27)

[†]Analysis performed using a negative binomial regression model with covariates of treatment group, smoking status, baseline % predicted FEV₁, number of exacerbations in previous year (as an ordinal variable), and geographic region (as defined for the study/ISE) with log (time in on- and off-treatment period) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions; [‡]Analysis model as in footnote “†” with an additional covariate of study; [¶]Kaplan-Meier estimate; [§]Estimated from a Cox proportional Hazards Model with covariates of treatment group, smoking status, baseline % predicted FEV₁, number of exacerbations in previous year (as an ordinal variable), and geographic region (as defined for the study/ISE); ^{††}Analysis model as in footnote “§” with an additional covariate of study; ^{††}Contains both on-treatment and off-treatment exacerbation data. MATINEE study with an extended follow-up period up to two years; ^{¶¶}CMH adjusted relative risk to placebo;

Abbreviations: BEC, blood eosinophil count; CI, confidence interval, CMH, Cochrane Mantel-Haenszel; ED, emergency department; FEV₁, forced expiratory volume in one second; ICS, inhaled corticosteroid; KM, Kaplan-Meier; LABA, long-acting beta₂-agonist; LAMA, long-acting muscarinic antagonist; mITT-300, modified intention-to-treat 300 (participants with BEC ≥300 cells/μL at screening who received ≥1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline); NA, not applicable; NR, not reported; PBO, placebo.

Company evidence submission for mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237]

2.6.3.4 Severe exacerbations

Annualised rate of severe exacerbations: In the MATINEE trial (21, 22), participants treated with mepolizumab resulted in a 34% reduction in the annualised rate of severe exacerbations (requiring hospitalisation and/or resulting in death) compared with placebo (Table 25). In the mITT-300 populations of the METREO and METREX trials (27), severe exacerbations were generally infrequent (27). Results from the pooled mITT-300 population (27), were consistent with the MATINEE trial (RR: [REDACTED] [95% CI: [REDACTED]] p=[REDACTED]) (Table 25).

Time-to-first severe exacerbation: In the MATINEE trial (21, 22), cumulative incidence as seen in the KM plot (Appendix J, Section J.5.2) showed that the probability of a first moderate/severe exacerbation was lower for the mepolizumab group compared with the placebo group over the course of the study (Table 25). The time-to-first event analysis showed a reduction in the risk of severe exacerbation for mepolizumab compared with placebo (HR: [REDACTED] [95% CI: [REDACTED]]; p=[REDACTED]) (Table 25). Consistent results showing the HR favoured mepolizumab treatment over placebo were observed across the mITT-300 population from the METREO and METREX trials (27) (Table 25). Results for of the pooled mITT-300 population (27) were consistent with MATINEE, with a HR of [REDACTED] (95% CI: [REDACTED]) p=[REDACTED] (Table 25).

Proportion of participants with at least one severe exacerbation: In the MATINEE trial (21, 22), a lower proportion of participants had at least one severe exacerbation following mepolizumab (11%) treatment compared with placebo (15%). The risk of having ≥ 1 severe exacerbation was numerically lower for participants treated with mepolizumab compared with placebo (relative risk: 0.78 [95% CI: 0.54, 1.11] p=0.166) (Table 25). Consistent results were observed across the individual trials (MATINEE (21, 22), METREO mITT-300 (27), and METREX mITT-300 (27) (Table 25). Similar results were also observed in the pooled mITT-300 population (27) with a relative risk of [REDACTED] (95% CI: [REDACTED]) p=[REDACTED] (Table 25).

Table 25: Pooled mITT-300 population (MATINEE mITT + METREO mITT-300 + METREX mITT-300): Severe exacerbations

	MATINEE		METREO mITT-300		METREX mITT-300		Pooled mITT-300	
	Mepo	PBO	Mepo	PBO	Mepo	PBO	Mepo	PBO
N	403	401	■	■	■	■	568	578
Rate of severe exacerbations								
Annualised rate of severe exacerbations (95% CI)	0.10	0.15	■	■	■	■	■	■
Rate ratio [†] (mepo/PBO) (95% CI)	0.66 (0.43, 1.01); p=0.055		■		■		■	
Time to first severe exacerbation								
Week 52 probability (%) of a severe exacerbation [¶] (95% CI)	■	■	■	■	■	■	■	■
Week 104 probability (%) of a severe exacerbation [¶] (95% CI)	■	■	■	■	■	■	■	■
HR [§] (mepo/PBO) (95% CI); p value	■		■		■		■	
Proportion of participants with ≥1 severe exacerbation								
Proportion of participants with ≥1 severe exacerbation ^{‡‡} , n (%)	46 (11)	59 (15)	■	■	■	■	■	■
Relative risk mepolizumab - placebo (95% CI); p value	0.78 (0.54, 1.11); p=0.166		■		■		■	

Source: MATINEE CSR (21); Sciurba 2025 (22); Data on File (pooled mITT-300 analysis) (27)

[†]Analysis performed using a negative binomial regression model with covariates of treatment group, smoking status, baseline % predicted FEV₁, number of exacerbations in previous year (as an ordinal variable), and geographic region (as defined for the study/ISE) with log (time in on- and off-treatment period) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions; [‡]Analysis model as in footnote “†” with an additional covariate of study; [¶]Kaplan-Meier estimate; [§]Estimated from a Cox proportional Hazards Model with covariates of treatment group, smoking status, baseline % predicted FEV₁, number of exacerbations in previous year (as an ordinal variable), and geographic region (as defined for the study/ISE); ^{††}Analysis model as in footnote “§” with an additional covariate of study; ^{‡‡}Contains both on-treatment and off-treatment exacerbation data. MATINEE study with an extended follow-up period up to two years; ^{¶¶}CMH adjusted relative risk to PBO.

Abbreviations: CI, confidence interval, CMH, Cochran Mantel-Haenszel; ED, emergency department; FEV₁, forced expiratory volume in one second; ICS, inhaled corticosteroid; KM, Kaplan-Meier; LABA, long-acting beta₂-agonist; LAMA, long-acting muscarinic antagonist; mITT-300, modified intention-to-treat 300 (participants with BEC ≥300 cells/μL at screening who received ≥1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline); NA, not applicable.

2.6.3.5 CAT

2.6.3.5.1 CAT total score responders

In the MATINEE trial (21, 22), the proportion of CAT responders at Week 52 was similar between the mepolizumab group (41%) and placebo group (46%) (Table 26). The results observed in the MATINEE trial were inconsistent with the results in the mITT-300 population of the METREO and METREX trials (Table 26), both of which showed a numerical trend for a higher proportion of CAT responders in the mepolizumab group compared with the placebo group. The pooled mITT-300 population (27) did not show a treatment effect on the proportion of CAT responders (OR: [REDACTED] [95% CI: [REDACTED]] p=[REDACTED]) (Table 26).

The cumulative distribution function (percentage of participants achieving different levels of improvement in CAT score) for change from baseline in CAT total score at Week 52 showed no difference between treatment groups in MATINEE, while a separation was observed for the mITT-300 population from the METREO and METREX trials (plots provided in Appendix J, Section J.5.2). Notably, baseline CAT scores in the placebo group were similar across the three trials; however, at Week 52 the proportion of responders was higher in the placebo arm of MATINEE (46%) compared with the mITT-300 population in the METREO and METREX trials ([REDACTED]% and [REDACTED]%, respectively). In contrast, the proportion of responders in the mepolizumab group was relatively consistent across the studies (41% [MATINEE] to [REDACTED]% [METREX mITT-300]).

Table 26: Pooled mITT-300 population (MATINEE mITT + METREO mITT-300 + METREX mITT-300): CAT total score responders (Week 52)

Response defined as a decrease in the CAT score ^{†,‡}	MATINEE ^{‡‡}		METREO mITT-300		METREX mITT-300		Pooled mITT-300	
	Mepo	PBO	Mepo	PBO	Mepo	PBO	Mepo	PBO
N	403	401	████	████	████	████	568	578
Week 52, n	391	394	████	████	████	████	████	████
Responder n (%)	162 (41)	180 (46)	████	████	████	████	████	████
Non-responder n (%)	220 (56)	206 (52)	████	████	████	████	████	████
No change/worsening n (%)	████	████	████	████	████	████	████	████
Withdrawal from study prior to visit n (%)	████	████	████	████	████	████	████	████
Missing visit	████	████	████	████	████	████	████	████
Imputed [¶] , n (%)	████	████	████	████	████	████	████	████
Odds ratio [§] mepo vs. PBO (95% CI); p value	0.81 (0.60, 1.09); p=0.161		████████████████		████████████████		████████████████	
Relative risk ^{¶¶} of response mepolizumab - placebo (95% CI) [¶]	0.92 (0.81, 1.05)		NA		NA		NA	

Source: MATINEE CSR (21); Sciruba 2025 (22); Data on File (pooled mITT-300 analysis) (27)

[†]A response was defined as a decrease of at least 2 points in the CAT score from baseline to Week 52; [‡]For the MATINEE trial, the difference between the trial groups was not significant. Therefore, the remaining end points in the hierarchical testing strategy were not assessed; [¶]Participants with an intercurrent event of either treatment interruption or treatment discontinuation related to the COVID-19 pandemic have data set to missing following the event. Missing data was imputed following a MAR assumption based on 2000 imputations; [§]Analysis performed using a logistic regression model with covariates of baseline score, geographic region (as defined for the study/ISE), smoking status (current vs. never/ex-smoker), and treatment group. Estimates combined using Rubin's rules (for the MATINEE trial and pooled mITT-300 population); ^{‡‡}Analysis model as in footnote "§" with an additional covariate of study; ^{‡‡‡}Includes visits up to Week 52 for the MATINEE trial; ^{¶¶¶}The relative risk was calculated in a post hoc analysis.

Abbreviations: CAT, COPD assessment test; CI, confidence interval, COPD, chronic obstructive pulmonary disorder; COVID-19, coronavirus disease 2019; ICS, inhaled corticosteroid; KM, Kaplan-Meier; LABA, long-acting beta₂-agonist; LAMA, long-acting muscarinic antagonist; MAR, missing at random; mITT-300, modified intention-to-treat 300 (participants with BEC ≥300 cells/μL at screening who received ≥1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline); NA, not applicable.

2.6.3.5.2 Analysis of change from baseline in CAT score

In the MATINEE trial, at Week 52, the adjusted mean reduction from baseline in CAT score was similar in both the treatment groups (Table 27). In the mITT-300 population of the METREO and METREX trials (27), treatment difference observed at Week 52 favoured mepolizumab over placebo (Table 27, plots provided in Appendix J, Section J.5.2). While the pooled mITT-300 population did not show a treatment effect on the adjusted mean reduction from baseline in CAT score (Table 27), the change from baseline estimates were consistent across the three trials (MATINEE (21, 22), METREO mITT-300 (23, 25), and METREX mITT-300 (23, 24)). Notably, baseline CAT scores in the placebo group were similar across the three trials (Table 27, plots provided in Appendix J, Section J.5.2), but at Week 52, the reduction in the placebo group in MATINEE (-2.5) was greater than observed in the mITT-300 population of the METREO and METREX trials (■ and ■, respectively [Table 27]). The change from baseline in the mepolizumab group in the MATINEE trial (-2.1) was consistent with the mITT-300 population of the METREO and METREX trials (Table 27, plots provided in Appendix J, Section J.5.2).

Table 27: Pooled mITT-300 population (MATINEE mITT + METREO mITT-300 + METREX mITT-300): Change from baseline in CAT score (Week 52)

Response defined as a decrease in the CAT score [‡]	MATINEE [†]		METREO mITT-300		METREX mITT-300		Pooled mITT-300	
	Mepo	PBO	Mepo	PBO	Mepo	PBO	Mepo	PBO
N	403	401	■	■	■	■	568	578
Visit: Week 52								
n1 [¶]	382	384	■	■	■	■	■	■
n2 [§]	338	338	■	■	■	■	■	■
LS mean (SE)	17.0 (0.34)	16.6 (0.34)	■	■	■	■	■	■
LS mean change (SE)	-2.1 (0.34)	-2.5 (0.34)	■	■	■	■	■	■
Difference ^{††} (mepolizumab - placebo) (95% CI); p value	0.4 (-0.52, 1.37); p=0.378		■		■		■	

Source: MATINEE CSR (21); Sciurba 2025 (22); Data on File (pooled mITT-300 analysis) (27)

[†]Includes visits up to Week 52 for the MATINEE trial; [‡]Estimates are based on weighting applied to each level of class variable determined from observed proportions. Intercurrent events of treatment interruption or treatment discontinuation related to the COVID-19 pandemic have data set to missing following the event. Missing data imputed as MAR using 2000 imputations; [¶]Number of participants with analysable data for one or more time points; [§]Number of participants with analysable data at the given time point; ^{††}Analysis performed using mixed model repeated measures with covariates of baseline score, geographic region (as defined for the study/ISE), smoking status (current vs. never/ ex-smoker) and treatment and visit, plus interaction terms for visit by baseline and visit by treatment group. ^{‡‡}Analysis model as in footnote “††” with an additional covariate of study

Abbreviations: CAT, COPD assessment test; CI, confidence interval, COPD, chronic obstructive pulmonary disorder; COVID-19, coronavirus disease 2019; ICS, inhaled corticosteroid; LABA, long-acting beta₂-agonist; LAMA, long-acting muscarinic antagonist; LS, least squares; MAR, missing at random; mITT-300, modified intention-to-treat 300 (participants with BEC ≥300 cells/μL at screening who received ≥1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline); SE, standard error.

2.6.3.6 St. George's Respiratory Questionnaire

2.6.3.6.1 SGRQ-C total responders

In the MATINEE trial (21, 22), the proportion of SGRQ responders (achieving ≥ 4 -point improvement in SGRQ score) at Week 52 was numerically higher in mepolizumab group (50%) compared with the placebo group (46%) (OR 1.17 [95% CI: 0.87, 1.57] $p=$ [REDACTED]) (Table 28). The cumulative distribution function for change from baseline in SGRQ score at Week 52 shows consistent separation between the mepolizumab and placebo groups (plots provided in Appendix J, Section J.5.2). Across the individual studies (MATINEE (21, 22), METREO mITT-300 (23, 25), and METREX mITT-300 (23, 24)), the mean baseline SGRQ-C total scores were similar between treatment groups (53.4 to 55.3 points) and were indicative of poor HRQoL (Table 28). A consistent trend, i.e., numerically higher SGRQ-C responders in the mepolizumab group compared with placebo group was observed across the three trials (MATINEE (21, 22), METREO mITT-300 (23, 25), and METREX mITT-300 (23, 24)). The cumulative distribution (percentage of participants achieving different levels of improvement in SGRQ-C score) for the change from baseline at Week 52 in SGRQ-C total score showed a consistent separate curve between the two treatment groups in MATINEE and in METREO mITT-300 but this was not seen in METREX mITT-300 (plots provided in Appendix J, Section J.5.2). Similar trends were observed in the pooled mITT-300 population: the proportion of SGRQ responders at Week 52 was numerically higher in mepolizumab group ([REDACTED]%) compared with the placebo group ([REDACTED]%; OR: [REDACTED] [95% CI: [REDACTED]] $p=$ [REDACTED]) (Table 28).

Response, defined as a decrease in the SGRQ† total score‡	MATINEE¶		METREO mITT-300		METREX mITT-300		Pooled mITT-300	
	Mepo	PBO	Mepo	PBO	Mepo	PBO	Mepo	PBO
N	403	401	■	■	■	■	568	578
Week 52, n	390	393	■	■	■	■	■	■
Responder† n (%)	195 (50)	179 (46)	■	■	■	■	■	■
Non-responder n (%)	186 (48)	206 (52)	■	■	■	■	■	■
No change/worsening n (%)	■	■	■	■	■	■	■	■
Withdrawal from study prior to visit n (%)	■	■	■	■	■	■	■	■
Missing visit	■	■	■	■	■	■	■	■
Imputed§, n (%)	■	■	■	■	■	■	■	■
Odds ratio†† mepolizumab vs. placebo (95% CI); p value	1.17 (0.87, 1.57); p=0.291		■; p=■		■; p=■		■; p=■	
Relative risk¶¶ of response mepolizumab SC vs. placebo (95% CI)	1.04 (0.91, 1.20)		NA		NA		NA	

†A response was defined as a decrease of at least 4 points in the SGRQ total score from baseline to Week 52; ‡The relative risk was calculated in a post hoc analysis; §SGRQ scores calculated from conversions applied to SGRQ-C scores (SGRQ-C manual March 2016); ¶Includes visits up to Week 52 for the MATINEE trial; §Participants with an intercurrent event of either treatment interruption or treatment discontinuation related to the COVID-19 pandemic have data set to missing following the event. Missing data imputed as MAR using 2000 imputations; ††Analysis performed using a logistic regression model with covariates of baseline score, geographic region (as defined for the study/ISE), smoking status (current vs. never/ex-smoker), and treatment group. Estimates combined using Rubin's rules (for the MATINEE trial and pooled mITT-300 analysis); †‡Analysis model as in footnote "††" with an additional covariate of study; ¶¶¶The relative risk was calculated in a post hoc analysis. Abbreviations: CAT, COPD assessment test; CI, confidence interval, COPD, chronic obstructive pulmonary disorder; COVID-19, coronavirus disease 2019; ICS, inhaled corticosteroid; LABA, long-acting beta2-agonist; LAMA, long-acting muscarinic antagonist; LS, least squares; MAR, missing at random; mITT-300, modified intention-to-treat 300 (participants with BEC ≥ 300 cells/ μ L at screening who received ≥ 1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline); NA, not applicable; SE, standard error.

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2.6.3.6.2 Analysis of change from baseline in SGRQ-C score

In the MATINEE trial (21, 22), at Week 52, the least squares (LS) mean change in SGRQ total score was –8.0 in mepolizumab group and –5.7 in placebo group (treatment difference –2.3 [95% CI: –4.64, 0.08] $p=0.059$) (Table 29). Across the individual trials (MATINEE (21, 22), METREX mITT-300 (27), and METREO mITT-300 (27)), the treatment difference observed at Week 52 favoured mepolizumab over placebo (Table 29). The pooled mITT-300 population (27) showed similar trends as seen in the MATINEE trial. At Week 52, the LS mean change in SGRQ total score was –7.1 in mepolizumab group and –4.9 in placebo group (treatment difference –2.2 [95% CI: –4.14, –0.24] $p=0.028$) (Table 29).

Table 29: Pooled mITT-300 population (MATINEE mITT + METREO mITT-300 + METREX mITT-300): Change from baseline in SGRQ-C score (Week 52)

Response defined as a decrease in the SGRQ-C score ^{‡,¶}	MATINEE [†]		METREO mITT-300		METREX mITT-300		Pooled mITT-300	
	Mepo	PBO	Mepo	PBO	Mepo	PBO	Mepo	PBO
N	403	401	■	■	■	■	568	578
Visit: Week 52								
n1 [§]	380	383	■	■	■	■	■	■
n2 ^{††}	337	336	■	■	■	■	■	■
LS mean (SE)	46.4 (0.85)	48.6 (0.85)	■	■	■	■	■	■
LS mean change (SE)	-8.0 (0.85)	-5.7 (0.85)	■	■	■	■	-7.1 (0.71)	-4.9 (0.70)
Difference ^{‡‡} (mepolizumab - placebo) (95% CI); p value	-2.3 (-4.64, 0.08); p=0.059		■		■		-2.2 ^{¶¶} (-4.14, -0.24); p=0.028	

Source: MATINEE CSR (21); Sciurba 2025 (22); Data on File (pooled mITT-300 analysis) (27)

[†]Includes visits up to Week 52 for the MATINEE trial; [‡]SGRQ scores converted from SGRQ-C scores (SGRQ-C manual March 2016); [¶]Estimates are based on weighting applied to each level of class variable determined from observed proportions. Intercurrent events of treatment interruption or treatment discontinuation related to the COVID-19 pandemic have data set to missing following the event. Missing data imputed as MAR using 2000 imputations; [§]Number of participants with analysable data for one or more time points; [§]Number of participants with analysable data at the given time point; ^{††}Analysis performed using mixed model repeated measures with covariates of baseline score, geographic region (as defined for the study/ISE), smoking status (current vs. never/ ex-smoker) and treatment and visit, plus interaction terms for visit by baseline and visit by treatment group. ^{¶¶}Analysis model as in footnote “§” with an additional covariate of study Abbreviations: CI, confidence interval, COPD, chronic obstructive pulmonary disorder; COVID-19, coronavirus disease 2019; ICS, inhaled corticosteroid; LABA, long-acting beta₂-agonist; LAMA, long-acting muscarinic antagonist; LS, least squares; MAR, missing at random; mITT-300, modified intention-to-treat 300 (participants with BEC ≥300 cells/μL at screening who received ≥1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline); SE, standard error; SGRQ-C, St. George's Respiratory Questionnaire – COPD specific.

2.6.3.6.3 SGRQ-C domain scores

In the MATINEE trial (21, 22), baseline SGRQ-C domain scores were similar across the treatment groups with the “Impact” domain having the lowest baseline scores. Over the treatment period, improvements from baseline in LS mean SGRQ-C domain scores were observed in both groups; improvements were numerically greater in the mepolizumab group (Table 30).

In the individual trials (MATINEE (21, 22), METREO mITT-300 (27), and METREX mITT-300 (27)), mean baseline SGRQ-C domain scores were similar between treatment groups across the studies and were indicative of poor HRQoL (Table 30). At Week 52, the “Symptom” domain scores in the mITT populations of the METREO and METREX trials were numerically greater in the mepolizumab group vs. placebo, compared with MATINEE (Table 30).

Similar trends in the SGRQ-C domain scores by “Activity”, “Impact” and “Symptom” were observed in the pooled mITT-300 population (27). Numerical improvements from baseline in LS mean SGRQ-C domain scores were observed in both groups. In the pooled mITT-300 population, the “Impact” domain had the lowest baseline scores; and the mean changes in the “Activity” domain scores were small in both treatment groups compared with the other domain scores (Table 30).

Table 30: Pooled mITT-300 population (MATINEE mITT + METREO mITT-300 + METREX mITT-300): SGRQ-C scores and change from baseline at Week 52

SGRQ-C† domain scores	MATINEE‡		METREO mITT-300		METREX mITT-300		Pooled mITT-300	
	Mepo	PBO	Mepo	PBO	Mepo	PBO	Mepo	PBO
	403	401	■	■	■	■	568	578
Baseline								
n	■	■	■	■	■	■	■	■
Symptom	■	■	■	■	■	■	■	■
Activity	■	■	■	■	■	■	■	■
Impact	■	■	■	■	■	■	■	■
Visit: Week 52								
n	■	■	■	■	■	■	■	■
Symptom	■	■	■	■	■	■	■	■
Activity	■	■	■	■	■	■	■	■
Impact	■	■	■	■	■	■	■	■
Week 52 change from baseline								
n	■	■	■	■	■	■	■	■
Symptom	■	■	■	■	■	■	■	■
Activity	■	■	■	■	■	■	■	■
Impact	■	■	■	■	■	■	■	■

Source: MATINEE CSR (21); Sciurba 2025 (22); Data on File (pooled mITT-300 analysis) (27)

†SGRQ scores calculated from conversions applied to SGRQ-C scores (SGRQ-C manual March 2016); ‡Includes visits up to Week 52 for the MATINEE trial.

Abbreviations: COPD, chronic obstructive pulmonary disorder; ICS, inhaled corticosteroid; LABA, long-acting beta₂agonist; LAMA, long-acting muscarinic antagonist; mITT-300, modified intention-to-treat 300 (participants with BEC ≥300 cells/μL at screening who received ≥1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline); SGRQ-C, St. George's Respiratory Questionnaire – COPD specific.

2.6.3.7 Evaluating Respiratory Symptoms (E-RS) in COPD

The proportion of E-RS: COPD responders and change from baseline in E-RS COPD score was only evaluated in the MATINEE trial (Table 21) therefore pooled results are not available for these outcomes.

2.7 Subsequent treatments used in the relevant studies

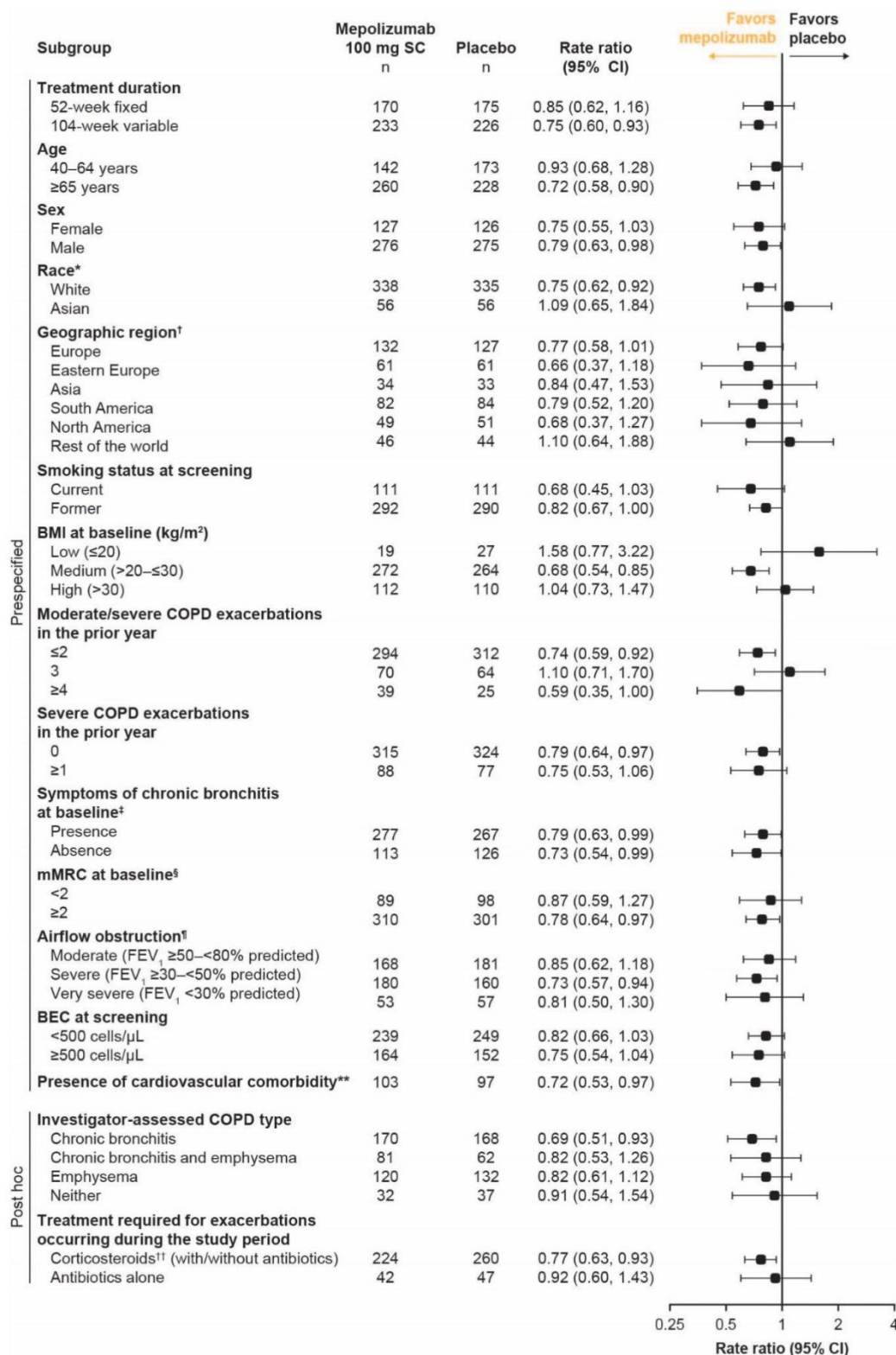
Not applicable.

2.8 Subgroup analysis

2.8.1 MATINEE

In MATINEE, the overall population showed a statistically significant reduction in the annualised rate of moderate/severe exacerbations with mepolizumab compared with placebo (21, 22). For the primary outcome of annual rate of moderate/severe exacerbations, the treatment effect of mepolizumab vs. placebo was generally consistent across key subgroups (Figure 10). Full subgroup results for the primary and secondary outcomes provided in Appendix C.

Figure 10: Subgroup analyses (MATINEE): Primary endpoint (annualised rate of moderate/severe exacerbations up to Week 104)



Source: Sciurba 2025 (22)

CIs have not been adjusted for multiplicity and should not be used for inference.

“African American/African heritage” and “Other” categories were not assessed due to small sample size ($n \leq 5$ in both treatment arms); “Other” includes American Indian or Alaskan native, Native Hawaiian or other Pacific Highlander and mixed race; †“Europe” includes Belgium, Denmark, France, Germany, Greece, Ireland, Italy, the Netherlands, Spain, Sweden, and the UK; “Eastern Europe” includes Hungary and Poland; “Asia” includes China, the Republic of Korea, and Taiwan; “South America” includes Argentina, Brazil and Mexico; “North America” includes Canada and the US; “Rest of the world” includes Australia, India, Israel, and New Zealand; ‡As assessed by responses at baseline to items related to cough and sputum in the SGRQ; §mMRC dyspnoea scale ranges from grade 0 to 4, with higher grades indicating more severe dyspnoea; ¶Classification based on postbronchodilator FEV₁ at screening, Global Initiative for Chronic Obstructive Lung Disease Reports for COPD; the “Mild” subgroup (FEV₁ $\geq 80\%$ predicted) was not assessed due to small sample size (2 patients with mepolizumab/3 with placebo); **Defined as any past or current diagnosis of myocardial infarction, coronary artery disease, angina pectoris, arrhythmia, or congestive heart failure; ††All administrations.

Abbreviations: BEC, blood eosinophil count; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; mMRC, modified Medical Research Council dyspnoea scale; SC, subcutaneous; SGRQ, St. George’s Respiratory Questionnaire; UK, United Kingdom; US, United States.

2.8.2 METREX mITT-300 and METREO mITT-300

No additional subgroup analyses from METREX and METREO were considered relevant for this appraisal, as the efficacy data reflective of the target population in this appraisal already reflect a predefined subgroup from within those trials, patients with a screening BEC ≥ 300 cells/ μ L.

2.8.3 Pooled analysis of data from MATINEE mITT, METREO mITT-300 and METREX mITT-300 (pooled mITT-300 population)

Subgroup analyses were conducted within the pooled mITT-300 population to assess the consistency of the treatment effect for the primary endpoint. The reduction in moderate/severe exacerbation rates with mepolizumab vs. placebo was generally consistent across most subgroups analysed. No subgroup showed a statistically significant effect in the opposite direction to the overall population, although some had wide CIs due to low participant numbers (Table 31). Subgroup results for the secondary outcomes are presented in Appendix C.

Table 31: Summary of subgroup analyses carried out on the primary endpoint (annualised rate of moderate/severe exacerbations) (pooled analysis of data from MATINEE, METREX mITT-300, and METREO mITT-300 [pooled mITT-300 population])

Subgroup	Mepo n	Mepo exacerbation rate/year	Placebo n	PBO exacerbation rate/year	Rate ratio (95% CI)
N	568		578		
Screening BEC					
<0.5 G/L	■	■	■	■	■
≥0.5 G/L	■	■	■	■	■
Age (years)					
40–<65	■	■	■	■	■
≥65	■	■	■	■	■
Sex					
Female	■	■	■	■	■
Male	■	■	■	■	■
Race					
African American/African heritage	■	–	■	–	–
White	■	■	■	■	■
Asian	■	■	■	■	■
Other	■	–	■	–	–
Geographic region					
Europe	■	■	■	■	■
United States	■	■	■	■	■
Rest of World	■	■	■	■	■
Exacerbations in the previous year					
≤2 exacerbations	■	■	■	■	■
3 exacerbations	■	■	■	■	■
≥4 exacerbations	■	■	■	■	■

Subgroup	Mepo n	Mepo exacerbation rate/year	Placebo n	PBO exacerbation rate/year	Rate ratio (95% CI)
Smoking status at screening					
Current	■	■	■	■	■
Never/former	■	■	■	■	■
Severity of airflow limitation (GOLD reports)					
Mild: ≥80% predicted	■	—	■	—	—
Moderate: ≥50%—<80% predicted	■	■	■	■	0.84 (0.64, 1.10)
Severe: ≥30%—<50% predicted	■	■	■	■	0.71 (0.59, 0.87)
Very severe: <30% predicted	■	■	■	■	0.98 (0.66, 1.44)
Symptoms of chronic bronchitis					
No	■	■	■	■	■
Yes	■	■	■	■	■
Symptoms of chronic bronchitis + screening BEC					
No symptoms + ≥500 BEC	■	■	■	■	■
Symptoms + ≥500 BEC	■	■	■	■	■
No symptoms + <500 BEC	■	■	■	■	■
Symptoms + <500 BEC	■	■	■	■	■

Source: Data on File (pooled mITT-300 analysis) (27)

Abbreviations: BEC, blood eosinophil count; CI, confidence interval; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mITT-300, modified intention-to-treat 300 (participants with BEC ≥300 cells/μL at screening who received ≥1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline; mepo, mepolizumab; PBO, placebo.

2.9 Meta-analysis

Beyond the MATINEE (21, 22) METREX (23, 24), and METREO (23, 25) trials and pooled mITT-300 analyses (27), no other data are available to assess the clinical effectiveness of mepolizumab as add-on maintenance treatment for adult patients with uncontrolled COPD of an eosinophilic phenotype despite treatment on a combination of an ICS, a LABA, and a LAMA. As a result, no additional meta-analyses were conducted.

A broader pooled population was created to inform the economic model, using IPD from two additional GSK studies, IMPACT (183) and ECLIPSE (184). As IMPACT and ECLIPSE did not include mepolizumab, they were not used to estimate treatment effects and are not discussed further in this section. Further detail on the broader pooled population is provided in Section 3.3).

2.10 Indirect and mixed treatment comparisons

In the absence of head-to-head RCTs, a matching-adjusted indirect comparison (MAIC) was performed to evaluate the efficacy of mepolizumab vs. dupilumab (166), which is currently being appraised by NICE (ACM2, 5 August 2025) for the maintenance treatment of uncontrolled COPD with raised blood eosinophils, and is included in the final scope of this appraisal (20). This approach was selected to account for between-study differences in baseline characteristics and eligibility criteria across the available trials. Note, safety was not tested as no differences vs. placebo were observed in the COPD trials for both mepolizumab and dupilumab (21, 24, 25, 170).

2.10.1 Brief description of the approach

A MAIC was conducted to estimate the relative efficacy of mepolizumab vs. dupilumab, using placebo as a common comparator. Individual patient data (IPD) from three clinical trials of mepolizumab (MATINEE (21), METREX (25), and METREO (24)) were weighted to match the aggregate baseline characteristics of patients in the published pooled analysis of the comparator trials. To ensure comparability, the analysis excluded MATINEE, METREX, and METREO participants who did not meet the BOREAS/NOTUS eligibility criteria, specifically, patients without CB (e.g. CB + emphysema or emphysema-only phenotypes), those with BEC <300 cells/ μ L at screening, mMRC <2, or post-bronchodilator FEV₁ outside the moderate-severe range (i.e. GOLD 4 or mild disease). These exclusions were applied for methodological alignment only, and it is acknowledged that efficacy signals were observed for mepolizumab in these groups in the mepolizumab trials (21-25) and/or pooled mITT-300 population (27).

The MAIC adjusted for key differences in patient characteristics, including age, sex, smoking status, eosinophil count, prior exacerbation history, and quality-of-life scores, to reduce bias from cross-trial heterogeneity. Treatment effects were then re-estimated in the weighted sample using methods consistent with the original trial analyses (e.g., negative binomial models for exacerbation rates, Cox models for time-to-event outcomes). Finally, indirect treatment comparisons (ITC) were performed using the Bucher method (190). This approach was chosen due to the lack of head-to-head trials and the availability of IPD for only one treatment (mepolizumab).

2.10.2 Study population and setting

The study population for the analyses described in this report is adults with a diagnosis of COPD and T2 inflammation characterised by an eosinophilic phenotype, and who frequently exacerbate despite treatment with optimised inhaled therapy.

Several major differences were identified regarding study eligibility criteria between the mepolizumab trials (METREO (23), METREX (23), and MATINEE and the dupilumab trials (NOTUS (170) and BOREAS (168)). These differences include the requirement of having CB symptoms, specific minimum blood eosinophil levels at and/or before screening, mMRC Dyspnoea Scale Score, and the severity of airflow limitation. To account for these differences and to make the analysis populations comparable, the ITC analysis populations from the MATINEE (23), METREX (23), and METREO (21, 22) trials were aligned to those of the BOREAS (168) and NOTUS (170) trials.

Specifically, the study populations were derived by applying the following additional inclusion criteria to the modified intention-to-treat populations of the mepolizumab trials:

- Include patients with BEC ≥ 300 cells/ μ L at screening (note that all patients in the MATINEE trial have a BEC ≥ 300 cells/ μ L at screening as per the inclusion criteria).
- Include patients with CB, based on two different definitions:
 - Definition #1 (applicable to the MATINEE (21, 22) trial data only): CB was determined based on investigator assessment at baseline; investigator assessed subtype is not available in METREO (23, 24) and METREX (23, 25) trials.
 - Definition #2 (applicable to the MATINEE (23, 24), METREX (23, 25) and METREO (21, 22) trial data): CB was determined based on responses to the cough and sputum items of the SGRQ-C questionnaire at baseline. Patients were

considered to have CB if they reported having a cough at least several days a week and sputum at least several days a week.

- Include patients with a mMRC Dyspnoea Scale Score of ≥ 2 at baseline (measured on a scale from 0 to 4)
- Include patients with moderate to severe airflow limitation at baseline, i.e., postbronchodilator FEV₁ predicted value $\geq 30\%$.

The patient populations obtained after applying the above criteria represent the analysis populations used for the ITCs between mepolizumab and dupilumab; these analysis populations will be referred to as “restricted populations”.

2.10.3 Evidence base

For mepolizumab, IPD from the MATINEE (23), METREX (23), and METREO (21, 22) trials were used. Relevant clinical trials for dupilumab were obtained from an SLR, where the NOTUS (170) and BOREAS (168) trials were identified. For the MAIC analyses described in this submission, aggregated data were used from the publication reporting on the pooled analysis of the BOREAS and NOTUS trials (191).

2.10.4 MAIC methodology

The main analytical approach was to use IPD from the MATINEE (23), METREX (23), and METREO (21, 22) trials and aggregate data from the NOTUS (170) and BOREAS (168) trials to indirectly compare mepolizumab with dupilumab considering placebo as the common comparator. This was performed using the MAIC method.

The objective of the MAIC was to obtain a homogeneous patient population across both mepolizumab and dupilumab trials and to adjust for the potential effect modifiers. This was achieved by re-weighting individual patients from the mepolizumab trials (MATINEE (21, 22), METREX (23), and METREO (23)) to match the mean baseline characteristics of patients enrolled in the comparator (dupilumab) trials (NOTUS (170) and BOREAS (168)).

The matching was accomplished by re-weighting patients in the mepolizumab trials based on their odds of having been enrolled in the respective comparator trials. This method aligns with the guidance set out in NICE Technical Support Document 18 (TSD 18) for population adjustment in the absence of IPD for comparator studies (192). While the approach is similar to propensity score weighting with the difference that IPD are not available for the comparator trials so that the usual maximum likelihood approach cannot be used to estimate the parameters of the propensity score

model. Instead, a method of moments must be used. Matching was performed separately for the active treatment and placebo arms.

The effective sample size (ESS) was computed as the square of the summed weights divided by the sum of the squared weights (193). If the weights are treated as fixed, this effective sample size provides the correct sample size for converting the standard deviation of the re-weighted outcome to a standard error (SE).

To estimate weighted relative treatment effects between mepolizumab and placebo after re-weighting patients in the mepolizumab trials (MATINEE (21, 22), METREX (23), and METREO (23)), similar methods as used in the primary trial analysis were used. SEs for MAIC estimates were calculated from these methods using the robust sandwich estimator. Sandwich estimators are empirically derived from the data, avoiding overly strong assumptions about the weights. This approach accounts for the fact that the weights are estimated rather than fixed and known. Wherever possible, this estimator was obtained using PROC GENMOD in SAS with patient weights entered through the WEIGHT option. Additionally, the REPEATED statement was used to ensure that the weights were correctly interpreted in the estimation of SEs.

Indirect treatment effects of mepolizumab vs. dupilumab were calculated using the Bucher method:

- For RRs, HRs and ORs, the respective ratio of mepolizumab vs. placebo (obtained from the MAIC) was divided by the respective ratio of dupilumab vs. placebo;
- For change from baseline in SGRQ-C total scores, the mean difference in change from baseline of dupilumab vs. placebo was subtracted from the mean difference in change from baseline of mepolizumab vs. placebo;
- In terms of calculation of 95% CIs around the indirect treatment effect estimates, the variance (the square root of which was used to calculate the CI) was equal to the variance of the direct comparison of mepolizumab vs. placebo plus the variance of the direct comparison of dupilumab vs. placebo. For ratio effect estimates (i.e. RR, HR, and OR), these calculations were done on a logarithmic scale.

In addition to MAICs that adjusted for the list of potential effect modifiers, unadjusted ITC was also conducted using the Bucher method (190).

2.10.5 Matching variables

The following variables were considered as potential confounders/effect modifiers and were thus adjusted for as matching variables in the MAICs:

- Age (in years, numerical)
- Sex (categorical; male vs. female)
- Race (categorical; White vs. not White)
- Geographic region (categorical; Asia vs. Latin America vs. Europe vs. Western Countries)
- BMI (categorical if possible; $<25 \text{ kg/m}^2$ vs. ≥ 25 to $<30 \text{ kg/m}^2$ vs. $\geq 30 \text{ kg/m}^2$)
- Number of moderate/severe exacerbation at baseline (numerical)
- Having ≥ 1 severe exacerbation at baseline (categorical)
- Smoking status (categorical; current vs. former)
- BEC at screening (numerical)
- SGRQ-C total score at baseline (numerical)
- E-RS:COPD score at baseline (numerical).

The following baseline characteristics were considered but not included in the MAIC analysis because they were not reported in all the relevant clinical trials: mMRC score, presence of CV disease and duration of COPD disease.

2.10.6 Calculation of weighted outcomes after matching

2.10.6.1 Calculation of rate ratio for annualised rate of moderate/severe exacerbations of COPD

Matching-adjusted exacerbation RRs were calculated from a negative binomial model adjusting for baseline covariates. The list of adjusted covariates was consistent with the approach used in the primary clinical trial analysis, i.e. treatment group, geographic region, smoking status, baseline post-bronchodilator percent-predicted FEV₁, number of moderate/severe exacerbations in previous year (≤ 2 , 3, ≥ 4 as ordinal)

PROC GENMOD in SAS based on the negative binomial distribution was used with patient weights entered through the WEIGHT option. The REPEATED statement was used to ensure that the weights are correctly interpreted in the estimation of SEs.

2.10.6.2 Calculation of hazard ratio for time to first exacerbation

Matching-adjusted HRs for time to first exacerbation used a Cox proportional hazard model allowing for baseline covariates adjustment. The list of adjusted covariates was consistent with the approach used in the primary clinical trial analysis i.e. treatment group, geographic region, smoking status, baseline post-bronchodilator percent-predicted FEV₁, number of moderate/severe exacerbations in previous year (≤ 2 , 3, ≥ 4 as ordinal).

PROC PHREG in SAS was used with patient weights entered through the WEIGHT option.

2.10.6.3 Calculation of odds ratio for SGRQ-C responder rate (improvement ≥ 4 points) at 52 weeks

Matching-adjusted ORs for SGRQ-C total score responders at Week 52 were calculated using a logistic regression model adjusting for baseline covariates. The list of adjusted covariates was consistent with the approach used in the primary clinical trial analysis, i.e. treatment group, smoking status, geographic region, and baseline score.

PROC GENMOD in SAS based on the logistic distribution was used with patient weights entered through the WEIGHT option. The REPEATED statement was used to ensure that the weights are correctly interpreted in the estimation of SEs.

2.10.6.4 Calculation of change in SGRQ-C total score from baseline to 52 weeks

Matching-adjusted estimates of change from baseline in the SGRQ-C scores was analysed using mixed model repeated measures (MMRM) adjusting for baseline covariates. The list of adjusted covariates was consistent with the approach used in the primary clinical trial analysis, i.e. treatment group, baseline value, smoking status, geographic region, visit/time, visit/time period by baseline, and visit/time period by treatment group.

PROC MIXED in SAS was used with patient weights entered through the WEIGHT option. PROC GENMOD was not used since it only provides valid estimates under the missing completely at random (MCAR) assumption, but not for missing at random (MAR).

2.10.7 Results

2.10.7.1 Descriptive summary statistics of baseline characteristics

Table 32 summarises the sample sizes across mepolizumab trials after applying the eligibility criteria in BOREAS/NOTUS trials (168, 170, 191) (i.e. BEC of ≥ 300 cells/ μL , presence of CB, mMRC score ≥ 2 , and moderate to severe airflow limitation). From MATINEE (21, 22), when CB was defined based on investigator assessment, the final sample sizes were 177 in the mepolizumab arm, and 157 in the placebo arm. From MATINEE (21, 22), METREX (23), and METREO (23), when CB was defined based on SGRQ-C responses at baseline, the pooled sample sizes were 266 in the mepolizumab arm, and 252 in the placebo arm.

Table 32: Summary of sample sizes in the mepolizumab trials

	MATINEE mITT		METREO mITT†		METREX mITT		Pooled mITT MATINEE mITT/ METREO mITT/ METREX mITT	
	Mepo	PBO	Mepo	PBO	Mepo	PBO	Mepo	PBO
mITT population	403	401	223	226	417	419	1,043	1,046
Restricted population – defining CB based on investigator assessment	■	■	■	■	■	■	■	■
Restricted population – defining CB based on SGRQ-C responses assessment	■	■	■	■	■	■	■	■

Source: Data on File (Matching-adjusted indirect comparison: final report) (166)

†The mepolizumab 300 mg SC dose is not included

Abbreviations: CB, chronic bronchitis; mITT, modified intention to treat; NA, not applicable; SC, subcutaneous; SGRQ-C, St. George's Respiratory Questionnaire – COPD specific version.

Table 33: Baseline characteristics in combined BOREAS/NOTUS trials and restricted populations of the MATINEE mITT trial

Characteristic	Combined BOREAS / NOTUS trials		Restricted population of MATINEE mITT trial – defining CB based on investigator assessment		Restricted population of MATINEE mITT trial after matching – defining CB based on investigator assessment – after MAIC	
	Dupilumab (N = 938)	PBO (N = 936)	Mepo (N = [REDACTED])	Mepo (N = [REDACTED])	Mepo (ESS = [REDACTED])	PBO (ESS = [REDACTED])
Age, Mean (SD)	65.1 (8.0)	65.0 (8.3)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Female, n (%)	320 (34.1%)	302 (32.3%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Male, n (%)	618 (65.9%)	634 (67.7%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Not White, n (%)	123 (13.1%)	123 (13.1%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
White, n (%)	815 (86.9%)	813 (86.9%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Asia, n (%)	67 (7.1%)	66 (7.1%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
East Europe, n (%)	361 (38.5%)	358 (38.2%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Latin America, n (%)	255 (27.2%)	256 (27.4%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Western Countries/High-income, n (%)	255 (27.2%)	256 (27.3%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
BMI < 25, n (%)	315 (33.6%)	317 (33.9%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
BMI 25 to < 30, n (%)	332 (35.4%)	352 (37.6%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
BMI ≥ 30, n (%)	291 (31.0%)	267 (28.5%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Duration of COPD (years), Mean (SD)	–	–	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Mod/Severe exacerbations, Mean (SD)	2.2 (1.0)	2.2 (0.9)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Severe exacerbations = 0, n (%)	696 (74.2%)	722 (77.1%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

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Characteristic	Combined BOREAS / NOTUS trials		Restricted population of MATINEE mITT trial – defining CB based on investigator assessment		Restricted population of MATINEE mITT trial after matching – defining CB based on investigator assessment – after MAIC	
	Dupilumab (N = 938)	PBO (N = 936)	Mepo (N = [REDACTED])	Mepo (N = [REDACTED])	Mepo (ESS = [REDACTED])	PBO (ESS = [REDACTED])
≥ 1, n (%)	242 (25.8%)	214 (22.9%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Current smokers, n (%)	276 (29.4%)	282 (30.1%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Former smokers, n (%)	662 (70.6%)	654 (69.9%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Baseline blood eosinophil count (Mean, SD)	0.524 (0.31)	0.535 (0.33)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
SGRQ-C total score at baseline (Mean, SD)	50.2 (17.4)	49.8 (17.2)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
E-RS:COPD score at baseline (Mean, SD)	13.2 (6.95)	13.1 (7.05)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Source: Data on File (Matching-adjusted indirect comparison: final report) (166)

Abbreviations: BMI, body mass index; CB, chronic bronchitis; COPD, chronic obstructive pulmonary disorder; E-RS:COPD, Evaluating Respiratory Symptoms in COPD; ESS, effective sample size; mITT, modified intention to treat; NA, not applicable; SC, subcutaneous; SD, standard deviation; SGRQ-C, St. George's Respiratory Questionnaire – COPD specific version.

Table 34: Baseline characteristics in the combined BOREAS / NOTUS trials and restricted populations of the pooled MATINEE / METREO / METREX trials

Characteristic	Combined BOREAS / NOTUS trials		Restricted population of pooled MATINEE / METREO / METREX trials – defining CB based on SGRQ-C responses at baseline		Restricted population of pooled MATINEE / METREO / METREX trials after matching – defining CB based on SGRQ-C responses at baseline – After MAIC	
	Dupilumab (N = 938)	PBO (N = 936)	Mepo (N = [REDACTED])	PBO (N = [REDACTED])	Mepo N = [REDACTED]; ESS = [REDACTED]	PBO (N = [REDACTED]; ESS = [REDACTED])
Age (years), Mean (SD)	65.1 (8.0)	65.0 (8.3)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Female, n (%)	320 (34.1%)	302 (32.3%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Male, n (%)	618 (65.9%)	634 (67.7%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Race – Not White, n (%)	123 (13.1%)	123 (13.1%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Race – White, n (%)	815 (86.9%)	813 (86.9%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Geographic region – Asia	67 (7.1%)	66 (7.1%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
East Europe	361 (38.5%)	358 (38.2%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Latin America	255 (27.2%)	256 (27.4%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Western Countries/High-income	255 (27.2%)	256 (27.3%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
BMI < 25, n (%)	315 (33.6%)	317 (33.9%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
BMI 25 to <30, n (%)	332 (35.4%)	352 (37.6%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
BMI ≥ 30, n (%)	291 (31.0%)	267 (28.5%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Duration of COPD (years), mean (SD)	–	–	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Number of moderate/severe	2.2 (1.0)	2.2 (0.9)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Company evidence submission for mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237]

Characteristic	Combined BOREAS / NOTUS trials		Restricted population of pooled MATINEE / METREO / METREX trials – defining CB based on SGRQ-C responses at baseline		Restricted population of pooled MATINEE / METREO / METREX trials after matching – defining CB based on SGRQ-C responses at baseline – After MAIC	
	Dupilumab (N = 938)	PBO (N = 936)	Mepo (N = [REDACTED])	PBO (N = [REDACTED])	Mepo N = [REDACTED]; ESS = [REDACTED]	PBO (N = [REDACTED]; ESS = [REDACTED])
exacerbations, mean (SD)						
Number of severe exacerbations at baseline, n (%)						
0	696 (74.2%)	722 (77.1%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
≥1	242 (25.8%)	214 (22.9%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Smoking status, n (%)						
Current smoker, n (%)	276 (29.4%)	282 (30.1%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Former smoker, n (%)	662 (70.6%)	654 (69.9%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Baseline BEC (Mean, SD)	0.524 (0.31)	0.535 (0.33)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
SGRQ-C total score (Mean, SD)	50.2 (17.4)	49.8 (17.2)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
E-RS:COPD score (Mean, SD)	13.2 (6.95)	13.1 (7.05)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Source: Data on File (Matching-adjusted indirect comparison: final report) (166)

Abbreviations: BEC, blood eosinophil count; BMI, body mass index; CB, chronic bronchitis; COPD, chronic obstructive pulmonary disorder; ERS:COPD, Evaluating Respiratory Symptoms in COPD; ESS, effective sample size; mITT, modified intention to treat; NA, not applicable; SC, subcutaneous; SD, standard deviation; SGRQ-C, St. George's Respiratory Questionnaire – COPD specific version.

Before any adjustment, when comparing the baseline characteristics of the restricted populations of mepolizumab trials with pooled dupilumab trials, several differences emerge. Compared to participants in the dupilumab arm, participants in the mepolizumab arm tended to be older, had a lower percentage with ≥ 1 severe exacerbation, had a higher proportion of trial participants from western countries and a lower proportion of trial participants from Eastern Europe, and reported worse baseline quality of life (as indicated by a higher mean SGRQ-C score). Distribution of baseline characteristics in the combined BOREAS / NOTUS and in restricted populations of mepolizumab trials are shown in Table 33 and Table 34.

Table 33 and Table 34 also present the baseline characteristics after applying MAIC weights in the restricted populations based on investigator-assessed CB and SGRQ-based CB, respectively. Since all the baseline variables shown were used as matching variables in the MAIC approach (except COPD duration, which was not reported for the combined BOREAS / NOTUS study population), the means of all continuous variables as well as the distribution for all categorical variables after weighting are the same as in the combined BOREAS / NOTUS study population.

2.10.7.2 Distribution of MAIC weights

The distribution of MAIC weights (rescaled), in the restricted population based on investigator-assessed CB, for mepolizumab and placebo arms are presented in Appendix K (Figure 1). The plot also shows that there were no extreme individual weights; there was no individual patient who contributed more than 5% to the sum of all weights.

The distribution of MAIC weights (rescaled), in the restricted population based on SGRQ-C defined CB, for mepolizumab and placebo arms are presented in Appendix K (Figure 2). The plot also shows that there were no extreme individual weights; there was no individual patient who contributed more than 5% to the sum of all weights.

2.10.7.3 MAIC estimates of mepolizumab vs. dupilumab

The results for MAIC estimates of mepolizumab vs. dupilumab, based on pooled BOREAS/NOTUS data for key exacerbation and QoL outcomes, are provided in Table 35. The histograms for MAIC weights and forest plots are provided in Appendix B.

In both the restricted population that defined CB based on investigator assessment, and the restricted population that defined CB based on SGRQ-C responses, after adjusting for baseline covariates, compared with dupilumab, mepolizumab demonstrated a numerically lower annualised rate of moderate/severe exacerbations (RR: 0.91 [95% CI: 0.6, 1.37] and RR: 1.13 [95% CI: 0.8, 1.58], respectively), annualised rate of severe exacerbations (RR 0.68

[95% CI: 0.27, 1.72], and RR: 1.01 [95% CI: 0.47, 2.16], respectively), as well as a lower hazard of first moderate/severe exacerbation (HR: 0.71 [95% CI: 0.46, 1.08], and (HR: 0.83 [95% CI: 0.61, 1.14], respectively. These differences were not statistically significant.

In addition, across both restricted populations, after matching on inclusion criteria and adjusting for baseline covariates, there was no statistically significant difference between mepolizumab and dupilumab in the change from baseline in SGRQ-C total score at Week 52, or SGRQ-C total score response at Week 52.

Table 35: ITC/MAIC estimates of mepolizumab vs. dupilumab

	Method	ESS		Relative estimate mepolizumab vs. placebo			ITC mepolizumab vs. dupilumab (pooled BOREAS / NOTUS)		
		N Mepo	N PBO	Rate ratio	95% CI LL	95% CI UL	ITC mepo vs. dupilumab rate ratio	95% CI LL	95% CI UL
Defining chronic bronchitis on investigator assessment (using restricted population from MATINEE trial) (estimates calculated from IPD)									
Annualised rate of moderate/severe exacerbations	Restricted population – ITC (unadjusted)	177	157	■	■	■	1.09	0.78	1.53
Annualised rate of moderate/severe exacerbations	Restricted population – MAIC†	80	101	■	■	■	0.91	0.60	1.37
Annualised rate of severe exacerbations	Restricted population – ITC (unadjusted)	177	157	■	■	■	1.04	0.47	2.30
Annualised rate of severe exacerbations	Restricted population – MAIC†	80	101	■	■	■	0.68	0.27	1.72
Time to first moderate/severe exacerbation	Restricted population – ITC (unadjusted)	177	157	■	■	■	0.93	0.65	1.32
Time to first moderate/severe exacerbation	Restricted population – MAIC†	80	101	■	■	■	0.71	0.46	1.08
Change from baseline for SGRQ-C total score at Week 52	Restricted population – ITC (unadjusted)	177	157	■	■	■	1.34	-2.62	5.3
Change from baseline for SGRQ-C total score at Week 52	Restricted population – MAIC†	80	101	■	■	■	1.04	-2.62	4.69

	Method	ESS		Relative estimate mepolizumab vs. placebo			ITC mepolizumab vs. dupilumab (pooled BOREAS / NOTUS)		
		N Mepo	N PBO	Rate ratio	95% CI LL	95% CI UL	ITC mepo vs. dupilumab rate ratio	95% CI LL	95% CI UL
SGRQ-C total score response at Week 52	Restricted population – ITC (unadjusted)	177	157	■	■	■	0.88	0.53	1.45
SGRQ-C total score response at Week 52	Restricted population – MAIC [†]	80	101	■	■	■	1.19	0.63	2.24
Defining chronic bronchitis based on SGRQ-C responses at baseline (using restricted population from pooled MATINEE mITT / METREO mITT / METREX mITT trials) (estimates calculated from IPD)									
Annualised rate of moderate/severe exacerbations	Restricted population – ITC	266	252	■	■	■	1.09	0.84	1.41
Annualised rate of moderate/severe exacerbations	Restricted population – MAIC [†]	150	159	■	■	■	1.13	0.80	1.58
Annualised rate of severe exacerbations	Restricted population – ITC	266	252	■	■	■	1.02	0.52	1.99
Annualised rate of severe exacerbations	Restricted population – MAIC [†]	150	159	■	■	■	1.01	0.47	2.16
Time to first moderate/severe exacerbation	Restricted population – ITC	266	252	■	■	■	0.89	0.67	1.17
Time to first moderate/severe exacerbation	Restricted population – MAIC [†]	150	159	■	■	■	0.83	0.61	1.14

	Method	ESS		Relative estimate mepolizumab vs. placebo			ITC mepolizumab vs. dupilumab (pooled BOREAS / NOTUS)		
		N Mepo	N PBO	Rate ratio	95% CI LL	95% CI UL	ITC mepo vs. dupilumab rate ratio	95% CI LL	95% CI UL
Change from baseline for SGRQ-C total score at Week 52	Restricted population – ITC	266	252	■	■	■	1.42	-1.88	4.71
Change from baseline for SGRQ-C total score at Week 52	Restricted population – MAIC†	150	159	■	■	■	1.70	-1.46	4.86
SGRQ-C total score response at Week 52	Restricted population – ITC	266	252	■	■	■	0.97	0.65	1.46
SGRQ-C total score response at Week 52	Restricted population – MAIC†	150	159	■	■	■	0.96	0.58	1.58

†Matching variables in MAIC include: Age, sex, race, geographic region, BMI, number of moderate/severe exacerbations at baseline, severe exacerbation, smoking status, blood eosinophil count at screening, and SGRQ-C total score at baseline. E-RS:COPD score at baseline was additionally adjusted for in analysis that defined CB based on investigator assessment.

Abbreviations, BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; E-RS,COPD, EXACT-Respiratory Symptoms for COPD; ESS, effective sample size; EXACT, Exacerbations of Chronic Pulmonary Disease Tool; IPD, individual patient-level- data; ITC, indirect treatment comparison; LL, lower limit; MAIC, matching-adjusted indirect comparison; SGRQ-C, Saint George Respiratory Questionnaire – COPD specific version; UL, upper limit.

2.10.8 Uncertainties in the indirect and mixed treatment comparison

This ITC compared the relative efficacy of mepolizumab and dupilumab in COPD, using data from the MATINEE (21, 22), METREX (23, 24), METREO (23, 25), BOREAS (168, 169), and NOTUS (170, 171) trials. By applying inclusion criteria from the BOREAS and NOTUS trials to the mepolizumab trials and subsequently adjusting for baseline characteristics using a MAIC, this study aimed to account for differences in patient populations across the clinical trials and create balanced and comparable analysis populations. The approach followed recognised methodological guidance (NICE TSD 18 (192)).

The ITC analysis showed that, after matching on inclusion criteria and adjusting for baseline covariates, there were no statistically significant differences between mepolizumab and dupilumab in terms of reducing the risk of exacerbations or improving HRQoL (SGRQ-C total score).

However, a trend favouring mepolizumab was observed in reducing the rate of severe exacerbations, particularly when CB was defined based on investigator assessment. Additionally, a trend favouring mepolizumab over dupilumab in reducing the time to first moderate/severe exacerbation was observed, regardless of the CB definition used in the analysis. While these differences were not statistically significant, they suggest a potential benefit of mepolizumab in reducing the severity and frequency of exacerbations.

Despite efforts to balance differences in eligibility criteria and measured baseline characteristics in our analysis, there remains the potential for unobserved or unmeasured confounders between the populations to bias the results.

It should also be noted that the MAIC necessarily excluded several subgroups of patients enrolled in the MATINEE, METREX, and METREO trials who were not eligible for the dupilumab trials, such as those without chronic bronchitis (e.g. CB + emphysema or emphysema-only phenotypes), with blood eosinophil counts <300 cells/ μ L at screening, with mMRC <2 , or with GOLD 4 airflow limitation. These groups had demonstrated efficacy benefits in the MATINEE, METREX, and METREO trials (see Section 2.6.1 and Section 2.6.3), but were omitted from the MAIC solely to align with the BOREAS/NOTUS trial populations. As a result, the MAIC findings reflect a restricted subset of patients rather than the broader MATINEE, METREX, and METREO trial population.

In conclusion, while no statistically significant differences were observed between mepolizumab and dupilumab for the outcomes analysed, the observed trends numerically favoured mepolizumab in reducing severe exacerbations and time to first moderate/severe

exacerbation. For health-related quality of life, as measured by the St. George's Respiratory Questionnaire (SGRQ), no clear trends were observed between treatments.

2.11 Adverse reactions

Mepolizumab has been studied in over 3,000 patients across 26 clinical trials in eosinophilic conditions and is approved for severe eosinophilic asthma, CRSwNP, EGPA, and hypereosinophilic syndrome (28). Of these, only severe eosinophilic asthma currently has a NICE recommendation (TA671 (194)). In addition to clinical trial data, mepolizumab has also been evaluated in real-world settings, including the prospective REALITI-A study, which confirmed a safety profile consistent with that observed in clinical trials (158). Mepolizumab's mechanism of action and safety profile are well established across indications, and this section presents safety data specific to the COPD population.

Safety data from the mepolizumab trials were not available specifically for the pooled mITT-300 population and were only available for the safety populations of the MATINEE (21, 22), METREX (23, 24), and METREO (23, 25) trials. However, this is not considered a limitation, because eosinophil count is a predictive biomarker of efficacy rather than of safety, and AE profiles are not expected to differ by eosinophil level. Therefore, the safety populations from the individual trials provide a robust and appropriate basis for evaluating the safety and tolerability of mepolizumab in patients with COPD.

2.11.1 MATINEE

2.11.1.1 Overall summary of AEs

All patients from MATINEE who received at least one dose of mepolizumab or placebo were included in the safety population. The mean duration of exposure to mepolizumab or placebo was approximately 15 months in the trial groups. No new safety concerns were identified in this study, and the safety outcomes in MATINEE remain consistent with the known safety profile of mepolizumab (22).

The overall incidence and event rate of on-treatment AEs, serious adverse events (SAE), and adverse events of special interest (AESI) were similar between the mepolizumab and placebo groups (Table 36). The overall incidence of on-treatment AEs considered by the investigator to be related to study treatment was similar between the treatment groups (5% in mepolizumab, 4% in placebo). AEs leading to treatment discontinuation were also similar between the two treatment arms (3% in mepolizumab, 4% in placebo). Fatal and nonfatal CV events were generally balanced between the trial groups; however, there were differences in

the number of patients who had heart failure (favouring placebo) and the number who had other CV events (favouring mepolizumab) (Table 36).

Table 36: Adverse events during or after the treatment period (safety population[†])

Adverse events n (%)	Mepo (N=403)	PBO (N=401)
Any event during the treatment period	299 (74%)	307 (77%)
Any event during or after the treatment period		
Overall	301 (75%)	308 (77%)
Event leading to treatment discontinuation	14 (3%)	18 (4%)
Event leading to withdrawal from the trial	15 (4%)	16 (4%)
Any serious adverse event or death during the treatment period	99 (25%)	112 (28%)
Death during or after the treatment period	11 (3%)	11 (3%)
Adverse events of special interest		
Systemic reaction during the treatment period [‡]	5 (1%)	5 (1%)
Local site reaction during the treatment period [‡]	2 (<1%)	3 (1%)
Cancer during the treatment period [¶]	8 (2%)	13 (3%)
Independently adjudicated MACE during or after the treatment period[§]	11 (3)	11 (3)
Death from a cardiovascular cause ^{††}	6 (1%)	3 (1%)
Nonfatal myocardial infarction	2 (<1%)	6 (1%)
Nonfatal stroke	3 (1%)	3 (1%)
Fatal or nonfatal myocardial infarction ^{††}	2 (<1%)	6 (1%)
Fatal or nonfatal stroke ^{††}	3 (1%)	3 (1%)

Source; Sciurba 2025 (22)

[†]The safety population included all the patients who underwent randomisation and received at least one dose of mepolizumab or placebo. In the analysis of the safety end points, the group in which a patient was included for analysis was based on whether the patient received more doses of mepolizumab or placebo; [‡]Systemic or local site reactions were identified by means of an electronic case-report form that was designed for the collection of data on systemic reaction or local injection-site reactions; [¶]Events were identified with the use of a standard *Medical Dictionary for Regulatory Activities*, version 27.0, query for "malignancies."; [§]In accordance with the statistical analysis plan, major adverse cardiovascular events (MACEs) were adjudicated on the basis of criteria provided in the clinical events classification charter, version 3; ^{††}Patients may have had multiple conditions leading to death and may have had multiple nonfatal events.

Abbreviations: MACE, major adverse cardiac event.

The most frequently reported on-treatment AEs in both groups were exacerbation or worsening of COPD, COVID-19, nasopharyngitis, headache, and pneumonia (Table 37) (22).

A summary of on- and post-treatment pneumonia events is provided in Table 38.

Company evidence submission for mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237]

The most common SAEs were exacerbation or worsening of COPD (in 11% and 14%, respectively) and pneumonia (in 3% and 3%, respectively) (Table 37). Death during or after the treatment period occurred in 11 patients (3%) in each treatment group; the cause of death was adjudicated by an independent committee that was unaware of trial-group assignments.

Table 37: MATINEE: Most common (≥5%) adverse events and most common (≥2%) serious adverse events on treatment (safety population)

Event n (%)	Mepo (n=403)	PBO (n=401)
Most common (≥5%) adverse events (on treatment)		
Exacerbation or worsening of COPD	49 (12)	62 (15)
COVID-19	50 (12)	49 (12)
Nasopharyngitis	41 (10)	32 (8)
Headache	31 (8)	27 (7)
Pneumonia	30 (7)	27 (7)
Back pain	26 (6)	26 (6)
Upper respiratory tract infection	25 (6)	20 (5)
Influenza	19 (5)	19 (5)
Dyspnoea	20 (5)	20 (5)
Arthralgia	22 (5)	16 (4)
Diarrhoea	22 (5)	12 (3)
Hypertension	17 (4)	27 (7)
Most common (≥2%) serious adverse events (on treatment)		
Exacerbation or worsening of COPD	46 (11)	55 (14)
Pneumonia	14 (3)	14 (3)

Source: Sciurba 2025 (22)

Abbreviations: COPD, chronic obstructive pulmonary disease; COVID-2019, coronavirus disease 2019.

Table 38: MATINEE: Summary of on- and post-treatment pneumonia events (safety population)

Event n (%)	Mepo (n=403)	PBO (n=401)
Any event	35 (9)	33 (8)
Infections and infestations	35 (9)	33 (8)
Pneumonia	30 (7)	31 (8)
Pneumonia bacterial	2 (<1)	1 (<1)
Atypical pneumonia	0	2 (<1)
COVID-19 pneumonia	1 (<1)	1 (<1)
Pneumonia pseudomonal	1 (<1)	1 (<1)
Pneumonia streptococcal	1 (<1)	0
Pulmonary tuberculosis	0	1 (<1)

Source: Sciurba 2025 (22)

Abbreviations: COVID-2019, coronavirus disease 2019.

Company evidence submission for mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237]

2.11.2 METREX and METREO (safety population)

2.11.2.1 Overall summary of AEs

In both trials, all patients who received at least one dose of mepolizumab or placebo were included in the respective trial safety populations. The incidence of AEs and SAEs was similar between the trial groups in METREX (23, 24) and METREO (23, 25) (Table 39). Deaths occurred (either during the treatment period or after discontinuation of the trial regimen) in 4% of patients in METREX (16/417 patients in the mepolizumab group and 17/419 patients in the placebo group) and in 3% of patients in METREO (4/223 patients in the mepolizumab group and 9/226 patients in the placebo group). In both trials, AEs leading to treatment discontinuation were similar between treatment arms (METREX: 7% in mepolizumab, 8% in placebo; METREO: 4% in mepolizumab, 12% in placebo).

The most commonly reported AEs that occurred during the treatment period in both trials were exacerbations or worsening of COPD, nasopharyngitis, headache, and pneumonia (Table 40). In METREX, systemic reactions and injection-site reactions occurred during the treatment period in 2% and 3% of patients, respectively, in the mepolizumab group; in METREO, systemic reactions and injection-site reactions occurred in 1% and 3% of patients, respectively, in the 100 mg mepolizumab group (Table 39). Similar incidences of these AEs occurred in the placebo groups (2% and 3%, respectively, in METREX, and 2% and 4%, respectively, in METREO).

Table 39: METREX and METREO: Overview of adverse events (safety population)

Event	METREX [†]		METREO ^{‡,¶}	
	Mepo (N=233)	PBO (N=229)	Mepo (N=223)	PBO (N=226)
Adverse events[§]				
Any event	332 (80)	342 (82)	191 (86)	185 (82)
Event leading to treatment discontinuation ^{††}	31 (7)	35 (8)	9 (4)	27 (12)
Event leading to withdrawal from trial	18 (4)	21 (5)	7 (3)	18 (8)
Any serious adverse event ^{¶¶}	115 (28)	131 (31)	57 (26)	68 (30)
Any death	16 (4)	17 (4)	4 (2)	9 (4)
Systemic or local site reaction during treatment period^{††}				
Systemic reaction	7 (2)	9 (2)	3 (1)	4 (2)

Event	METREX [†]		METREO ^{‡,¶}	
	Mepo (N=233)	PBO (N=229)	Mepo (N=223)	PBO (N=226)
Injection-site reaction	12 (3)	12 (3)	6 (3)	10 (4)

Source: Pavord 2017 (23)

[†]The METREX overall safety population included patients who received at least one dose of mepolizumab or placebo; [‡]The METREO safety population included patients who received at least one dose of mepolizumab or placebo; [¶]The mepolizumab 300 mg dose was not included; [§]Events (including fatal events) that occurred during the treatment period or after discontinuation of the trial regimen are shown; ^{††}p<0.05 for the between-group differences in METREO (analysis was performed post hoc); ^{‡‡}Systemic or local site reactions were identified by means of an electronic case-report form that was designed for the collection of data on systemic reactions or local injection-site reactions. There were no reports of anaphylaxis that were considered by the investigator to represent a systemic reaction meeting Sampson's criteria for anaphylaxis. One patient in the METREO 300-mg mepolizumab group (modified intention-to-treat population) reported an anaphylactic reaction to diclofenac; the reaction resolved, and the patient continued the trial regimen.

Abbreviations: mepo, mepolizumab; PBO, placebo.

Table 40: METREX and METREO: On-treatment AEs occurring in ≥5% patients (safety population)

Event	METREX [†]		METREO ^{‡,¶}	
	Mepo (N=233)	PBO (N=229)	Mepo (N=233)	PBO (N=229)
COPD exacerbation or worsening	76 (18)	74 (18)	28 (13)	35 (15)
Nasopharyngitis	64 (15)	63 (15)	39 (17)	48 (21)
Headache	42 (10)	56 (13)	34 (15)	20 (9)
Pneumonia	29 (7)	37 (9)	24 (11)	22 (10)
Back pain	33 (8)	31 (7)	15 (7)	11 (5)
Oropharyngeal pain [§]	24 (6)	18 (4)	15 (7)	4 (2)
Upper respiratory tract infection	21 (5)	21 (5)	16 (7)	21 (9)
Influenza	16 (4)	24 (6)	6 (3)	11 (5)
Cough	22 (5)	15 (4)	14 (6)	12 (5)
Pain in extremity	19 (5)	16 (4)	7 (3)	5 (2)
Arthralgia	13 (3)	19 (5)	10 (4)	6 (3)
Sinusitis	19 (5)	13 (3)	8 (4)	7 (3)
Dyspnoea	17 (4)	12 (3)	12 (5)	18 (8)
Diarrhoea	18 (4)	15 (4)	16 (7)	14 (6)
Bronchitis	9 (2)	12 (3)	8 (4)	9 (4)
Pyrexia	18 (2)	13 (3)	6 (3)	10 (4)
Pharyngitis	12 (3)	18 (4)	5 (2)	4 (2)
Injection-site reactions	12 (3)	12 (3)	6 (3)	10 (4)

Source: Pavord 2017 (23)

[†]Safety-All population: patients receiving ≥1 dose of mepolizumab or placebo; [‡]The METREO safety population included patients who received at least one dose of mepolizumab or placebo; [¶]The mepolizumab 300 mg dose was not included; [§]Oropharyngeal Pain: p<0.05 for between-group differences in METREO (post hoc analysis).

Abbreviations: AE, adverse events; COPD, chronic obstructive pulmonary disease; mepo, mepolizumab; PBO, placebo.

Table 41: METREX and METREO: On-treatment and off-treatment pneumonia events (safety population)

Events n (%)	METREX [†]		METREO ^{‡,¶}	
	Mepo (N=233)	PBO (N=229)	Mepo (N=233)	PBO (N=229)
Any event	40 (10)	44 (11)	26 (12)	27 (12)
Infections and infestations [§]				
Pneumonia	35 (8)	41 (10)	26 (12)	25 (11)
Lung infection	2 (<1)	2 (<1)	0	0
Pneumonia klebsiella	1 (<1)	0	0	0
Pneumonia streptococcal	1 (<1)	0	0	0
Pneumonia pseudomonal	0	0	0	0
Pneumonia bacterial	0	0	1 (<1)	0
Pneumonia haemophilus	0	0	0	1 (<1)
Pneumonia necrotising	0	0	0	1 (<1)
Pneumonia pneumococcal	0	0	1 (<1)	0
Pneumonia staphylococcal	0	0	1 (<1)	0
Pulmonary tuberculosis	0	0	0	0
Respiratory, thoracic and mediastinal disorders				
Broncho pneumopathy	0	1 (<1)	0	0
Pneumonitis	1 (<1)	0	0	0
Pneumonia aspiration	0	0	1 (<1)	0

Source: Pavord 2017 (23)

[†]Safety-All population: patients receiving ≥1 dose of mepolizumab or placebo; [‡]The METREO safety population included patients who received at least one dose of mepolizumab or placebo; [¶]The mepolizumab 300 mg dose was not included; [§]Pneumonia events include both on- and post-treatment events based on a group of relevant preferred

Abbreviations: mepo, mepolizumab; SC, subcutaneous.

2.12 Ongoing studies

The pivotal trials relevant to this indication, MATINEE (21, 22), METREX (23, 24) and METREO (23, 25), have been presented in this submission and report mature data.

One multi-country, prospective, non-interventional study (REALITI-C) of mepolizumab in adults with COPD and newly prescribed treatment in routine clinical practice is ongoing. This study is designed to collect real-world data on the effectiveness, and treatment patterns of mepolizumab and is being conducted across multiple regions, including the UK (should mepolizumab receive regulatory approval and reimbursement). A summary overview of REALITI-C is provided in Table 42.

Company evidence submission for mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237]

Table 42: Summary overview of REALITI-C

Category	Details
Study type	Global, prospective, non-interventional study
Population	The study will be conducted in adult patients ≥ 40 years of age with newly prescribed mepolizumab as add-on therapy per country-specific label for the treatment of COPD. This is a global study and will include countries across different regions, including North America and Europe. Additional regions and countries may be added to this study following local approval of mepolizumab for the treatment of COPD.
Treatment decision	At treating physician's discretion, independent of study inclusion
Inclusion criteria	- To participate in this study patients must meet all of the following inclusion criteria at enrolment: ≥ 40 years of age at enrolment - Documented diagnosis of COPD for at least 12 months, as per physician's judgment - Confirmed availability of medical records for at least 12 months prior to inclusion in the study - Newly initiated treatment with add-on mepolizumab for COPD with an eosinophilic phenotype or characterized by raised blood eosinophils (as per the country-specific label for COPD) as indicated below. Physician's decision to treat the patient with add-on mepolizumab was made independently of the patient's participation in the study (as per standard of care) - Initiated mepolizumab within 7 days before study enrolment (i.e., date of consent) OR prescribed with mepolizumab and is expected to initiate mepolizumab within 30 days after study enrolment (i.e., date of consent) - Patient has been on maintenance inhaled therapy prior to enrolment per country specific label - Patient is willing and able to complete study-related questionnaires - Patient provides voluntary signed informed consent to participate in the study before inclusion in the study.
Exclusion criteria	- Patients who meet any of the following criteria at enrolment are not eligible to participate in this study: - Patient has received mepolizumab for treating COPD more than 7 days prior to the enrolment. - Patient has received mepolizumab for indications other than COPD anytime within 12 months prior to the enrolment. - Patient has a documented history of failure with an anti-IL-5/5r therapy, per physician judgment, for any indication - Patient has any condition that, in the opinion of the investigator, may interfere with the patient's ability to participate in the study (such as short life expectancy, substance abuse, severe cognitive impairment, or other comorbidities that can predictably prevent the patient from completing visits and assessments as per SoC) - Patient currently participates in any interventional clinical trial

Category	Details
Primary objective	Change in annualised rate of moderate/severe exacerbations (12 months post- vs. pre-mepolizumab initiation)
Key secondary objectives	- Change in health status (SGRQ-C, CAT) at Months 3, 6, 12, 24, and 36 from baseline - Change in annualised rate of moderate/severe exacerbations at 24 & 36 months (vs. 12 month pre-exposure period) - Change in FEV₁ at Months 6, 12, 24, and 36 from baseline [REDACTED] - Describe the real-world treatment patterns of mepolizumab (including adherence, persistence, discontinuation rate, and reasons for discontinuation) - Evaluate the change in COPD-related HCRU, including annualised rate of hospital admissions, ED visits, and clinic/outpatient visits in the 12-month, 24-month, and 36-month periods post-mepolizumab initiation compared to the 12-month pre-exposure period - Evaluate the change in exposure to systemic corticosteroids at Months 6, 12, 24, and 36 from baseline
Exploratory objectives	- Evaluate the change in all-cause HCRU, including annualised rate of hospital admissions, ED visits, and clinic/outpatient visits in the 12-month, 24-month, and 36-month periods post-mepolizumab initiation compared to the 12-month pre-exposure period - Evaluate the change in BEC at Months 6, 12, 24, and 36 from baseline - Evaluate the change in lung function measured by FVC at Months 6, 12, 24, and 36 from baseline
Data collection schedule	Routine care: Enrolment, 6, 12, 24, 36 months PROs: Enrolment, 3, 6, 12, 24, 36 months
Spirometry	Mandatory in US and Canada
Index date	Date of first mepolizumab dose (Day 1)
Study conduct	No additional visits required; data collected during routine COPD visits. Sites will be asked to enter data at enrolment, Month 6 (±1 month), 12 (±3 months), 24 (±3 months), and 36 (±3 months) from index date. Patients will be asked to complete PROs at enrolment, Month 3 (±1 month), 6 (±1 month), 12 (±3 months), 24 (±3 months), and 36 (±3 months) from index date.
Expected results	Final: After 36-month follow-up

Source: REALITI-C (195)

Abbreviations: BEC, blood eosinophil count; CAT, COPD assessment test; COPD, chronic obstructive pulmonary disorder; ED, emergency department; ERS, European Respiratory Society; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; HCRU, healthcare resource use; PRO, patient reported outcomes; SGRQ-C, St. George's Respiratory Questionnaire – COPD specific version; US, United States.

2.13 Interpretation of clinical effectiveness and safety evidence

The evidence base for mepolizumab in COPD is drawn from three randomised, double-blind, placebo-controlled trials: the pivotal MATINEE trial (21, 22) and the mITT-300 subgroups from METREX and METREO trials (23-25, 27, 34) which were combined in a pooled analysis (27). All three individual trials were assessed as low risk of bias. The trials enrolled patients with frequent exacerbations (defined as ≥ 2 moderate exacerbations and ≥ 1 severe exacerbation in the previous 12 months), despite maximal inhaled triple therapy (ICS + LABA + LAMA, consistent with current UK SoC), and compared mepolizumab SC Q4W with placebo. The primary clinical focus across the programme was the prevention of exacerbations, reflecting mepolizumab's anti-IL-5 mechanism of action, which targets eosinophilic airway inflammation (196), a recognised driver of exacerbations in the target population.

2.13.1 Comparison vs. standard of care

MATINEE (21, 22) prospectively enrolled patients with a BEC ≥ 300 cells/ μ L at screening and ≥ 150 cells/ μ L in the prior year, alongside a high exacerbation burden. In METREO (23, 24), eligibility required BEC ≥ 150 cells/ μ L at screening or ≥ 300 cells/ μ L in the prior 12 months. In METREX (23, 25), there was no minimum BEC requirement for eligibility; however, patients were randomised into a high stratum (BEC ≥ 150 cells/ μ L at screening or ≥ 300 cells/ μ L in the prior 12 months) and a low stratum (BEC < 150 cells/ μ L at screening and < 300 cells/ μ L in the prior 12 months). The pooled mITT-300 population (27) included all MATINEE participants plus those from METREX and METREO with BEC ≥ 300 cells/ μ L at screening. While these post-hoc criteria more closely align with MATINEE, the broader original thresholds from these studies mean the pooled set may include a small proportion without a historical BEC ≥ 150 cells/ μ L, potentially capturing transient rather than persistent eosinophilia. However, most patients with BEC ≥ 300 cells/ μ L at screening are still likely to meet the historical BEC threshold (197), and results were consistent across trials, making any impact on findings unlikely. Other minor entry differences, such as the smoking history requirement (not applied in METREO), stricter asthma exclusion in MATINEE, and slightly different qualifying exacerbation definitions, reflect methodological variation rather than substantive differences in the target population.

The trial populations reflect a clinically important subgroup seen in UK practice: patients with uncontrolled eosinophilic COPD on triple therapy with frequent exacerbations. European real-world data indicate that ~6% of triple-therapy patients meet the trial BEC and exacerbation criteria, with UK patients showing very similar demographics, BMI, smoking status, and

exacerbation history to the MATINEE and pooled mITT-300 analysis populations (23). The comparator (placebo added to optimised triple therapy) reflects NICE-recommended care.

Against this backdrop, the clinical programme consistently demonstrated that adding mepolizumab to triple therapy delivers meaningful reductions in exacerbation risk and related outcomes. Across MATINEE (21, 22) and the pooled mITT-300 analysis (27), a consistent pattern of benefit was observed with mepolizumab in COPD patients with raised blood eosinophils and experiencing frequent exacerbations. In MATINEE (21, 22), mepolizumab significantly reduced the annualised rate of moderate/severe exacerbations by 21% compared with placebo, and significantly delayed the time to first moderate/severe exacerbation by 98 days (1, 2). Mepolizumab also reduced the annualised rate of exacerbations leading to ED visits and/or hospitalisations by 35% up to Week 104, a nominally significant finding due to the statistical hierarchy (1, 2). These effects were sustained for up to 104 weeks and were generally consistent across subgroups. The pooled mITT-300 analysis (27) further confirmed statistically significant reductions in exacerbation rates and delayed time to first exacerbation, supporting the findings of the pivotal trial.

HRQoL outcomes showed a trend of improvement in the mepolizumab group, but with no statistically significant differences compared with placebo. At Week 52, the proportion of SGRQ responders (≥ 4 -point improvement) was 50% with mepolizumab vs. 46% with placebo (OR 1.17 [95% CI: 0.87, 1.57]), with treatment effects directionally consistent across timepoints (Weeks 12, 24, 36, and 52). Mean change from baseline in SGRQ total score at Week 52 was numerically greater with mepolizumab vs. placebo (-5.7 [95% CI: -7.4 , -4.0]), particularly in patients with GOLD Stage 2 disease, although between-group differences were not statistically significant. EQ-5D-3L and visual analogue scale (VAS) scores showed small numerical improvements with mepolizumab, but these were not statistically significant. Similar trends were observed in pooled results (mITT-300 population): the proportion of SGRQ responders at Week 52 was numerically higher in the mepolizumab group compared with the placebo group, and a statistically significant improvement in SGRQ from baseline was observed in the mepolizumab group (27). Lung function remained stable and similar between groups, as expected for an anti-inflammatory therapy (21, 22, 27).

Reducing exacerbations is a central goal in COPD management due to their impact on morbidity, healthcare utilisation, and mortality (14, 15, 38, 47). The benefits observed with mepolizumab are consistent with this priority and its anti-IL-5 mechanism of action. Safety findings were favourable across all studies (21-25), with no new safety signals and AE rates comparable to placebo over follow-up periods of up to 104 weeks.

2.13.2 Comparison vs. dupilumab

Given the evolving treatment landscape, and the ongoing NICE appraisal for dupilumab (ACM2, 5 August 2025), it is considered the most relevant active comparator for mepolizumab. Mepolizumab and dupilumab are both SC biologics that target eosinophilic inflammation through distinct but related pathways: mepolizumab inhibits IL-5, while dupilumab blocks IL-4 and IL-13. Both are intended for use to reduce exacerbation rates in a similar COPD patient population: adults with frequent exacerbations and elevated BEC despite optimised inhaled maintenance therapy. The licensed indication and target population for mepolizumab closely mirrors the anticipated positioning of dupilumab, including baseline use of triple therapy and a history of exacerbations.

In the absence of head-to-head RCTs, a MAIC was conducted to assess the relative efficacy of mepolizumab vs. dupilumab. After aligning inclusion criteria and adjusting for baseline characteristics, no statistically significant differences were observed between treatments in moderate/severe exacerbation rates or HRQoL indicating at least broadly similar efficacy. Nonetheless, numerical trends favoured mepolizumab across several exacerbation outcomes. In particular, mepolizumab was associated with lower rates of severe exacerbations in patients with investigator-defined CB, and longer time to first moderate/severe exacerbation under both CB definitions. However, for health-related quality of life, as measured by the St. George's Respiratory Questionnaire (SGRQ), outcomes were comparable, with no clear trends observed between treatments.

The MAIC necessarily excluded several subgroups of patients enrolled in the mepolizumab programme (e.g. without CB, GOLD 4 disease, or BEC <300 cells/ μ L) that were not eligible for the dupilumab trials, where benefit was demonstrated for mepolizumab vs. placebo. In addition, mepolizumab is administered Q4W compared with Q2W for dupilumab, which may reduce treatment burden, support adherence, and offer potential QoL advantages. Taken together, these considerations support the appropriateness of a cost comparison scenario within the submission alongside the core cost-effectiveness case.

2.13.3 Conclusions

Mepolizumab offers a targeted anti-IL-5 therapy for patients with uncontrolled eosinophilic COPD on maximal inhaled triple therapy, a population with limited treatment options. Overall, results from the pivotal MATINEE trial (21, 22), supported by the pooled mITT-300 analysis (27) which included all MATINEE participants and relevant METREX and METREO subgroups (BEC $\geq$ 300 cells/ μ L at screening), provide a robust evidence base demonstrating the efficacy and safety of mepolizumab in COPD patients with frequent exacerbations and an eosinophilic

COPD phenotype. These benefits were consistent across trials and are directly applicable to UK clinical practice, supporting mepolizumab as an effective, well-tolerated treatment option for this defined patient group. A MAIC vs. dupilumab showed no statistically significant differences in overlapping populations, however mepolizumab demonstrated numerically better trends in key exacerbation outcomes, while HRQoL, as measured by the SGRQ, was broadly comparable between treatments, with no clear trends observed. Taken together with the benefits demonstrated in additional subgroups, these results suggest that mepolizumab may offer at least similar or greater overall health benefits. Moreover, mepolizumab is administered Q4W, which may reduce treatment burden and align better with patient preference, which in turn can support adherence and persistence with therapy (31). A study investigating patient-determined attributes of COPD treatment (including UK, US, and German patients) found that lower frequency of use was among the favoured attributes for current treatment, and that most participants would consider a switch in medication, mainly for improved efficacy, but also to reduce medication frequency (30). Improved adherence is particularly important in COPD, where comorbidities and polypharmacy already contribute to high treatment burden (32). In addition, less frequent dosing has the potential to ease clinic capacity pressures, particularly where initial injections are administered under supervision to monitor for adverse reactions.

3 Cost effectiveness

The cost effectiveness analysis demonstrates that mepolizumab is a cost-effective option compared with standard of care (SoC) and dupilumab.

- The economic analysis considered adult patients with uncontrolled COPD of an eosinophilic phenotype on a combination of an ICS, LABA, and a LAMA.
- The analysis utilises a *de novo* Markov model, developed in Excel, to reflect the impact of COPD exacerbations on outcomes across a lifetime horizon. Reduction in exacerbations is considered the primary treatment goal and the most important determinant of health outcomes for this population, with risks of mortality and further exacerbation varying by exacerbation severity and time since previous exacerbation (15, 47).
- Exacerbations are distinguished in the model by severity (moderate, severe) and tracked in order to assess the short-term and long-term impact of exacerbations on mortality, healthcare resource use, health-related quality of life, and future risk of exacerbations. The model includes 13 health states characterised by exacerbation severity and time since exacerbations, with 12 equivalent discontinuation health states.
- Where appropriate, pooled data from the MATINEE, METREX, METREO (mITT-300 trials), IMPACT, and ECLIPSE studies has been used to populate model inputs for SoC. The pooled mITT-300 trials have been used to estimate the treatment effect for mepolizumab, whilst dupilumab outcomes are informed by the MAIC.
- A stopping rule is included in the model at 52-weeks whereby only patients who are considered responders to treatment remain on mepolizumab. Responders are defined as patients who experience either:
 - Fewer severe exacerbations than the year prior
 - An equal number of severe exacerbations, and no increase in moderate exacerbations than the year prior.
- HRQoL data is informed by pooled EQ-5D-3L data from the MATINEE, METREX, METREO, and IMPACT studies, cross-walked from EQ-5D-5L to EQ-5D-3L where needed, in line with NICE guidelines (198, 199). Age-adjustment was applied to utility values.
- Cost and healthcare resource use estimates were aligned with the dupilumab NICE submission where appropriate (20), with costs updated using data from the most recently available year.
- Using the Patient Access Scheme (PAS) price for mepolizumab, base-case results show that mepolizumab is associated with an ICER of £18,347 compared with SoC, which is below the £20,000 per QALY WTP threshold. Dupilumab (at list price) is dominated by mepolizumab in the base-case pairwise analysis.
- Sensitivity/scenario analyses results are highly congruent with the deterministic analysis, with a probabilistic ICER of £18,383 compared with SoC. This is also true for 17 of the 19 scenario analyses performed for the comparison of mepolizumab with SoC, with the remaining two scenario analyses relating to the testing of shorter time horizons. At list price, dupilumab is dominated by mepolizumab across all but one of the scenario analyses (with mepolizumab still being cost-effective for the other scenario). Key model drivers from the OWSA include factors impacting the baseline exacerbation rates for severe exacerbations, and mepolizumab treatment effect for severe exacerbations.
- A cost-comparison scenario is also provided for the comparison of mepolizumab with dupilumab, given that the MAIC showed no statistically significant differences and either

favourable or comparable numerical trends in exacerbation outcomes for mepolizumab, indicating at least similar or greater health benefit.

- Over a 10-year time horizon, mepolizumab is associated with a cost-saving of £[REDACTED] when compared with the dupilumab list price.
- Overall, the cost-effectiveness analysis demonstrates the potential for mepolizumab to be a well-tolerated, cost-effective addition to existing SoC in the NHS for patients with uncontrolled COPD with an eosinophilic phenotype, with three large, robust clinical trials demonstrating a significant reduction in exacerbations for patients receiving mepolizumab vs. SoC. The cost-effectiveness and cost-comparison analyses showed that mepolizumab is a less costly alternative when compared to the list price of dupilumab.

3.1 Published cost-effectiveness studies

An SLR was conducted on 14th October 2016 and 17th May 2018, and subsequently updated on 25th July 2024, and 18th August 2025 to identify economic evaluations (cost-effectiveness and/or HCRU and costs studies) in patients with moderate, severe or very severe COPD treated with triple therapy (ICS/LABA+LAMA) or dual therapy with add on therapies. A detailed description of the SLR methods, full results and quality assessment of the identified economic evaluations is presented in Appendix E.

A total of 48 economic evaluations reporting cost-effectiveness analyses were identified by the SLR. The PRISMA flow diagram and full list of included publications are provided in Appendix E. In total, the evidence base comprised predominantly cost-utility analyses (CUA), with additional cost-effectiveness analyses (CEA) and partial economic evaluations including cost-minimisation analyses (CMA), budget impact analyses (BIA), and benefit–harm analyses. Time horizons varied across studies, ranging from short-term (1–3 years) to longer-term horizons of 20 years and lifetime models. Most analyses were conducted from single-country payer perspectives, including England, Scotland, Canada, and Germany. Treatments assessed spanned a broad range of inhaled regimens, most notably the cost-effectiveness of single-inhaler triple therapy (fluticasone furoate/umeclidinium/vilanterol [FF/UMEC/VI]) compared with multiple-inhaler triple therapy or dual therapies, as well as evaluations of budesonide/glycopyrronium/formoterol fumarate (BGF MDI 320) and earlier initiation of triple therapy. Other analyses included assessments of dual bronchodilator regimens and broader comparisons of therapy sequences. A tabulated summary of included economic evaluations reporting cost-effectiveness analyses is provided in Appendix E.

None of the included economic evaluations evaluated mepolizumab compared with standard of care or dupilumab for the patients with moderate, severe or very severe COPD treated with triple therapy (ICS/LABA+LAMA) or dual therapy with add on therapies. At the time the SLR

was conducted, the NICE appraisal of dupilumab had not concluded and was therefore not included in the SLR.

3.2 Economic analysis

No existing economic evaluations of mepolizumab vs. dupilumab or SoC were identified in the SLR; it was therefore necessary to develop a *de novo* cost effectiveness model (CEM) for the purpose of this appraisal.

Economic evaluations of other COPD therapies included in the SLR vary considerably in how they represent disease progression and exacerbations. Broadly, three types of model structures can be identified:

- Severity-only models (sometimes split by exacerbation history)
- Risk-equation models, and
- Direct exacerbation health state models (either with or without severity states).

Several HTA submissions and pharmacoeconomic reviews (e.g. NICE, SMC, CDA-AMC) and recent trial-based models adopt these approaches in applied decision-making contexts. As noted in Section 3.1, at the time the SLR was conducted, the NICE appraisal of dupilumab (20) had not yet concluded and was therefore not included in the SLR. However, interim committee papers and draft guidance were publicly available and were reviewed to ensure that insights were appropriately considered.

Most published evaluations use severity-only frameworks, typically Markov or semi-Markov cohort models in which patients transition between GOLD-defined lung function categories (moderate, severe, very severe) and death. Exacerbations are generally treated as events influencing costs and utilities but are not represented as discrete health states in the majority of evaluations. This “severity-only” framework has been applied in numerous evaluations, including roflumilast (200-203), triple therapy and dual therapy comparisons (204-208), and other analyses across multiple jurisdictions (208-216). Discrete event simulation (DES) models such as those by Hoogendoorn *et al.*, (217, 218) also fall into this category, since exacerbations were incorporated as events rather than structural health states (45, 219, 220). While severity-only models align with the traditional natural history of COPD, their reliance on airflow limitation categories provides only a partial view of the disease, as the acute and long-term burden of exacerbations is not structurally embedded. Across the published cost-effectiveness evidence, modelled populations were most commonly patients with moderate-to-very severe COPD, frequently with a history of exacerbations or chronic bronchitis. Only a

small number of analyses included mild disease states, and there is no clear evidence that disease severity differed substantially across models. However, differences in inclusion criteria, such as the use of elevated blood eosinophil counts (which represents a distinct subgroup with increased exacerbation risk) in more recent appraisals, may limit comparability with earlier evaluations.

A number of studies have used risk-equation models, most prominently the GALAXY COPD disease progression framework. These models apply linked risk equations to predict outcomes such as lung function decline, exacerbation risk, mortality, and QoL, based on baseline characteristics and treatment effects. They have been applied across the UK, Canadian, and Spanish settings (221-231), as well as in more recent trial-based analyses such as Beeh *et al.*, 2025 (222) using INTREPID trial data in Germany. CDA-AMC pharmacoeconomic reviews (2018: FF/UMEC/VI; 2021: BGF MDI 320) also relied on GALAXY-based analyses to inform their reimbursement recommendations. While these models represent an advance over severity-only structures by capturing multiple dynamic drivers of disease, exacerbations are treated as predicted outcomes rather than discrete health states. Beyond GALAXY, Ahmadian *et al.*, 2023 (232) developed a microsimulation whole-disease model where exacerbations were central to outcomes but still represented through predictive functions. Overall, risk-equation models improve flexibility and realism but can require extensive data across various outcomes to yield robust estimates and importantly do not fully capture exacerbations as structural determinants of disease burden, which is pivotal to capture in the target population of COPD patients in this appraisal.

Other evaluations have explicitly incorporated direct exacerbation health states, recognising exacerbations as structural determinants rather than secondary events. These models define states by both lung function and exacerbation severity or frequency, enabling short- and long-term consequences of exacerbations to be directly captured. Notably, the NICE appraisal (20) and SMC dupilumab appraisal (219) captured both lung function and exacerbation health states (where within COPD states patients can also transition between exacerbation health states). This combined structure was considered appropriate for reflecting COPD progression and treatment effects, recognising that exacerbations are a major driver of clinical and economic outcomes in COPD. Other evaluations include:

- Miravitlles *et al.*, 2020 (233) which used a seven-state Markov model combining COPD severity with separate moderate and severe exacerbation states.
- Lakhotia *et al.*, 2020 (234) which defined patients as infrequent or frequent exacerbators in a simplified Markov model

- Treharne *et al.*, 2021 (235) which used a semi-Markov model incorporating both airflow limitation and exacerbation history
- Martin *et al.*, 2022 (236) which distinguished severity states according to recent exacerbation history, and Trigueros *et al.*, 2022 (215)
- Liu *et al.*, 2022 (237), and Noorduynd *et al.*, (238) which extended severity-based models with explicit exacerbation sub-states.
- Wang *et al.*, 2023 (239) which also incorporated recent exacerbation status within a hybrid decision-tree/Markov structure
- Mountain *et al.*, 2024 (240) which used a whole-disease microsimulation framework to conduct a benefit–harm analysis of earlier triple therapy initiation, where exacerbations were explicitly tracked as core determinants of benefit.

Collectively, these approaches reflect a shift away from reliance on GOLD categories toward frameworks in which exacerbations themselves form health states, consistent with evidence that exacerbations drive lung function decline, increase mortality risk, worsen quality of life, and generate the majority of COPD-related costs.

3.2.1 Patient population

In line with the decision problem, and the patient populations considered for inclusion in the mepolizumab trials (outlined in Section 2.3), the cost-effectiveness analysis conducted for this appraisal considers adult patients with uncontrolled COPD (defined as ≥ 2 moderate or ≥ 1 severe exacerbations within 12 months) of an eosinophilic phenotype (defined as ≥ 300 cells/ μ L) on a combination of an ICS, a LABA, and a LAMA.

3.2.2 Model structure

A *de-novo* CEM was developed in Microsoft Excel using a Markov model structure.

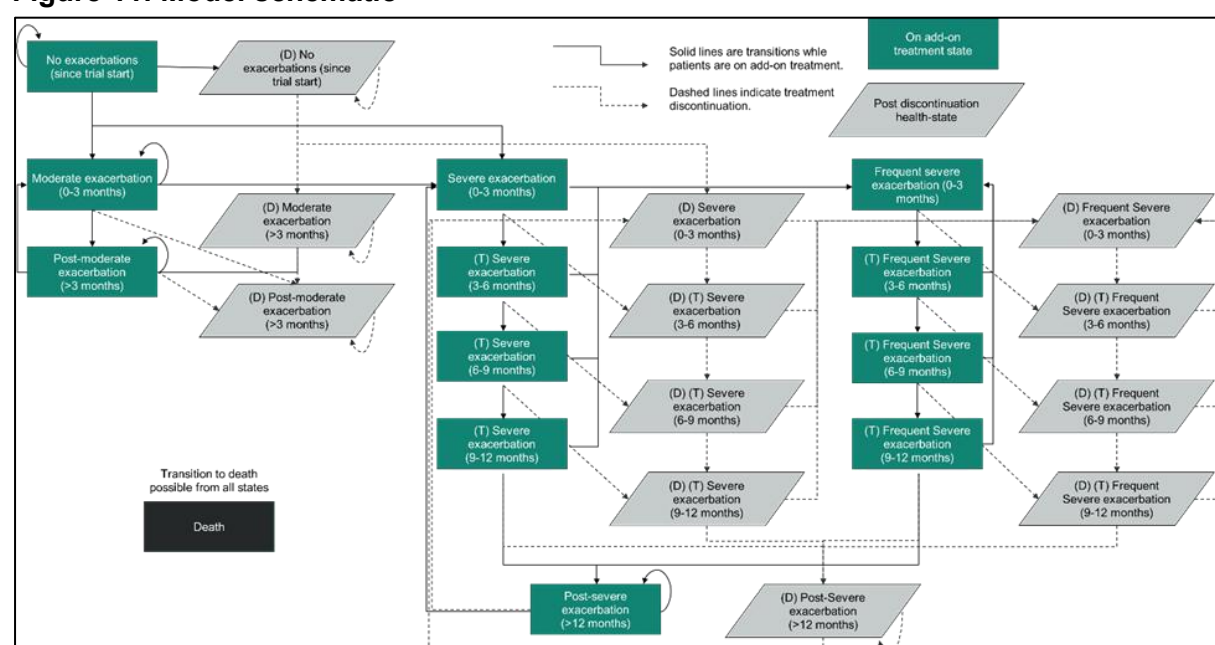
The model structure (Figure 11) is intended to reflect the impact of COPD exacerbations on outcomes across a lifetime horizon. Exacerbation events accelerate the deterioration of lung function and further increase the risk of future exacerbations and mortality in patients with COPD (241-244). Reduction in exacerbations is considered the primary treatment goal and the most important determinant of health outcomes for this population of COPD patients. This has been confirmed through consultations with clinical experts, including at a recent GSK advisory board (September, 2025) (20, 245).

Exacerbations in the model are distinguished by severity (moderate, severe) and tracked, in order to assess the short-term and long-term impact of exacerbations on mortality, HCRU, Company evidence submission for mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237]

HRQoL, and future risk of exacerbations. All patients enter the model in the ‘no exacerbations’ health state where they remain until they either experience their first exacerbation event (moderate or severe), discontinue from active treatment, or die. Severe and moderate exacerbations are captured in separate health states, while discontinuation from active treatment moves a patient to parallel health states (marked “(D)” in Figure 11). Frequent-severe health states are also included for patients who experience a second (or more) severe exacerbation within 12 months of their first. Patients who discontinue treatment with mepolizumab or dupilumab are assumed to receive SoC and are assigned an exacerbation risk and impact similar to patients who start on SoC treatment.

A description of each model health state is outlined in Table 43.

Figure 11: Model schematic



Note: a proportion of patients in the severe exacerbation health state (and associated tunnel states) will experience a moderate exacerbation (additional resource use). (D) – indicates a post-discontinuation health state, (T) indicates a tunnel state which will empty at the end of each model cycle.

Table 43: Health states included in the CEM

Health state	Description
No exacerbations since start of treatment	Captures patients experiencing no moderate or severe exacerbations since the time of starting treatment
Moderate exacerbation (0–3 months)	Management until resolution and short-term impact following a moderate exacerbation
Post-moderate exacerbation (≥3 months)	Long-term impact following a moderate exacerbation
Severe exacerbation (0–3 months)	Management until resolution and short-term impact following a severe exacerbation
Tunnel states following severe exacerbation (3– <6 months, 6– <9 months)	Captures medium-term impact associated with a single severe exacerbation in a 12-month period

Health state	Description
months, and 9– <12 months following severe exacerbation)	
Post-severe exacerbation (≥ 12 months)	Captures long-term impact following a severe exacerbation
Frequent severe exacerbation (0–3 months)	Management until resolution and short-term impact following a second (or more) severe exacerbation <12 months after most recent severe exacerbation
Tunnel states following frequent severe exacerbation (3– <6 months, 6– <9 months, and 9– <12 months following a second (or more) severe exacerbation)	Captures medium-term impact following second (or more) severe exacerbation within 12 months of a prior severe exacerbation
Discontinuation health states	Only included in mepolizumab and dupilumab treatment arms, a set of states parallel to each on-treatment health state to receive and follow patients that discontinue from their mepolizumab treatment
Death	Accumulating state for patients following death

Abbreviations: CEM, Cost-effectiveness model.

3.2.2.1 Moderate exacerbations

Following a first moderate exacerbation, patients enter the ‘moderate exacerbation (0–3 months)’ health state. This health state captures the short-term impact of a moderate exacerbation on HRQoL, HCRU and the possible increased probability of experiencing a subsequent moderate or severe exacerbation.

Patients in the ‘moderate exacerbation (0–3 months)’ health state can:

- Return to ‘moderate exacerbation (0–3 months)’ for the next cycle, if they have another moderate exacerbation
- Transition to the ‘Severe exacerbation (0–3 months)’ state, if they experience a severe exacerbation
- Transition to the ‘post moderate exacerbation (≥ 3 months)’ state, if they remain exacerbation free
 - Patients in this state continue to be at risk of another exacerbation each cycle
- Transition to the corresponding discontinuation (D) states, if they discontinue mepolizumab or dupilumab treatment
- Transition to the Death state, which is an absorbing state in the model.

Evidence in the literature suggests that patients experiencing a moderate exacerbation in the past year are more likely to experience either another moderate exacerbation or a severe exacerbation (246). This increased risk is captured in the model, both in the first cycle following

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the event ('moderate exacerbation 0–3 months'), and subsequent cycles reflecting the adjusted risk of additional exacerbations following an initial exacerbation.

3.2.2.2 Severe exacerbations

Severe exacerbations are defined as an exacerbation requiring in-patient hospitalisation (i.e., ≥ 24 hours). In the model, patients who experience a severe exacerbation from the moderate exacerbation or no exacerbation states transition to the 'Severe exacerbation (0–3 months)' state. This health state captures the short-term impact of a severe exacerbation on HRQoL, mortality risk, HCRU and the possible increased probability of experiencing a subsequent severe exacerbation. From this state, patients can:

- Transition through a series of tunnel states characterised by the time since their severe exacerbation, if they do not experience a further exacerbation
- Transition to 'Frequent severe exacerbations (0–3 months)', if they experience another severe exacerbation
- Transition to the corresponding discontinued (D) states, if they discontinue mepolizumab or dupilumab treatment
- Transition to the Death state.

The model assumes that a severe exacerbation is a more significant factor in predicting patient outcomes than a moderate exacerbation (requiring treatment with oral/systemic corticosteroids and/or antibiotics). Therefore, patients cannot return to the 'moderate exacerbation (0–3 months)' state.

If patients remain exacerbation-free and alive for 12 months, they will transition to the 'Post-severe exacerbation (>12 months)' state. From this state, patients experiencing a further severe exacerbation return to the 'Severe exacerbation (0–3 months)' state.

3.2.2.3 Frequent-severe exacerbations

Frequent-severe exacerbations are defined as two severe exacerbations within a 12-month period. Patients in the 'Frequent severe exacerbations (0–3 months)' state are associated with a higher utility decrement, an increased risk of mortality and further subsequent exacerbations, and increased HCRU (247, 248). Similar to the severe exacerbation health states, patients in this state can transition through several tunnel states, discontinue, or die. Patients who remain exacerbation-free and alive for 12 months, transition to the 'Post-severe exacerbation (>12 months)' state.

3.2.2.4 Discontinuation

Patients who discontinue treatment in the model move to a discontinued (D) health state. Discontinued (D) health states mirror the on-treatment health states, with new exacerbations impacting transitions between states. Transition probability values in the discontinued (D) health states are equal to those of the SoC arm (background therapy). Discontinued (D) health states are included to specify appropriate risks of mortality, exacerbations, and HRQoL/HCRU weights for those who are no longer receiving active biologic treatment. It is assumed that patients cannot experience an exacerbation and discontinue during the same cycle; instead, patients will discontinue in the next cycle, as it is clinically unlikely that a patient experiencing an exacerbation would discontinue treatment in the same time frame. It is assumed that once a patient has entered a discontinued (D) health state, they do not move back into the on-treatment health states.

3.2.2.5 Mortality

Patients can transition to the absorbing 'Death' state from any other model health state. Patients in the model are at risk of background mortality, with excess COPD mortality risk applied depending on the exacerbation health state patients are in.

3.2.2.6 Key features of the economic analysis

The key features of the economic analysis are summarised in Table 44.

In total, two previous NICE appraisals (ID6235 (20) and TA461 (45)) were available to inform the current evaluation (Table 44).

Table 44: Features of the economic analysis

	Previous evaluations		Current appraisal	
	ID6235 (20) (dupilumab)	TA461 (45) (roflumilast)	Chosen values	Justification
Patient population	Adults with COPD with raised EOS (≥ 300 cells/ μ L) who have uncontrolled disease (≥ 2 moderate or ≥ 1 severe historical exacerbations within 12 months) on triple inhaled therapy (LABA + LAMA + ICS) or double therapy (LABA + LAMA) where ICS is not appropriate	Patients with severe COPD, chronic bronchitis and ≥ 2 exacerbations in the previous year	Adult patients with uncontrolled COPD (defined as ≥ 2 moderate or ≥ 1 severe exacerbations within 12 months) of an eosinophilic phenotype (defined as ≥ 300 cells/ μ L) on a combination of an ICS, a LABA, and a LAMA	In line with the NICE final scope (41) and the expected marketing authorisation for mepolizumab (Appendix A)
Model Structure	Trial period: Decision tree Post-trial period: Markov model with 13 health states characterised by COPD GOLD severity stage and exacerbation status	Markov model with 3 health states (Severe COPD, very severe COPD and death)	Markov model with 13 health states characterised by exacerbation severity and time since exacerbation; 12 mirror discontinuation health states are also included.	Clinical experts consulted by GSK stated that exacerbations are the most important outcome in this population of COPD patients and that an exacerbation focused model is appropriate. Risks of further exacerbation vary by exacerbation severity and time since previous exacerbation (15, 47).
Time Horizon	Lifetime (35 years)	Lifetime (40 years)	Lifetime (30 years)	In line with NICE guidance (199)
Cycle Length	12 months	1 month	3 months	To reflect the progressive nature of COPD, and the event risks following an exacerbation
Discounting	3.5% for costs and outcomes	3.5% for costs and outcomes	3.5% for costs and outcomes	In line with NICE guidance (199)
Perspective	NHS and PSS	NHS and PSS	NHS and PSS	In line with NICE guidance (199)
Treatment effect waning	Dupilumab – 2-year waning on the treatment effect for lung function decline (FEV_1). No	NR	No treatment effect waning on the exacerbation treatment effect	In line with the dupilumab NICE submission assumptions for exacerbation rates and

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	Previous evaluations		Current appraisal	
	ID6235 (20) (dupilumab)	TA461 (45) (roflumilast)	Chosen values	Justification
	waning on the exacerbation treatment effect.			MATINEE trial 2-year follow up (20)
Source of utilities	Mapped SGRQ to EQ-5D from the pooled BOREAS and NOTUS studies, disutilities from the NOTUS study Cross-walked using Hernandez-Alava (2020) and age-adjusted using HSE 2014	COPD severity from Rutten van Molken (2006), disutilities from Rutten van Molken (2009)	Mapped EQ-5D-5L from the pooled MATINEE, METREX, METREO, and IMPACT studies to EQ-5D-3L (where required), Hernandez-Alava tariff used, disutilities also from the pooled trials (excluding ECLIPSE)	Pooled data increases the number of observations for utility analysis. EQ-5D data was not collected in the ECLIPSE study. Hernandez-Alava tariff used in line with NICE guidance (198)
Source of costs	Resource use frequencies and unit costs for health states and moderate exacerbations are derived from the NICE NG115 COPD economic model report, with unit costs from NHS Reference Costs 2022/23. Resource use frequencies for severe exacerbations are derived from the HES database, with unit costs from NHS Reference Costs 2022/23.	NR	Resource use frequencies and unit costs for health states are derived from the NICE NG115 COPD economic model report, with unit costs from NHS Reference Costs 2023/24. Resource use frequencies for severe exacerbations are derived from the HES database, with unit costs from NHS Reference Costs 2023/24 (249).	In line with the dupilumab NICE submission (20) and the expected resource use cost to the NHS

Abbreviations: COPD, chronic obstructive pulmonary disease; EOS, eosinophils; FEV, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HES, hospital episode statistics; ICS, inhaled corticosteroids; ID, in development; LABA, long-acting β_2 agonist; LAMA, long-acting muscarinic antagonist; NG, NICE guidance; NHS, National Health Service; NICE, National Institute of Healthcare and Excellence; NR, not reported; SCRQ, St George's Respiratory Questionnaire; TA, technology appraisal.

3.2.3 Intervention technology and comparators

3.2.3.1 Intervention

Mepolizumab is an add-on maintenance treatment for COPD patients with an eosinophilic phenotype, administered as a 100 mg SC injection Q4W in combination with background therapy. This is in line with the dosing schedule in the mepolizumab trials, and the SmPC (Appendix A). Background therapy is assumed to be triple therapy (ICS+LAMA+LABA), in line with the NG115 (19), and the mepolizumab trial populations as outlined in Section 2.3. The GOLD report also recommends triple therapy for patients with BEC of ≥ 300 (10) which aligns with the patient population considered in this appraisal (Section 1.1).

The specific background therapies used in the model are a weighted basket based on 2023 data from IQVIA's Hospital Pharmacy Audit, as outlined in Table 45.

Table 45: Background therapy weightings

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

Source: NICE Dupilumab (ID6235) 2025 (20).

3.2.3.2 Comparators

Standard of care is represented by triple therapy, as outlined in Section 3.2.3.1. This is the primary comparison (and most robust comparison for decision making) in the cost-effectiveness analysis.

Dupilumab, administered as a 300 mg SC dose Q2W in combination with background therapy (represented by triple therapy), is included as an exploratory analysis in the cost-effectiveness model, given that it is currently being appraised by NICE (ACM2, 5 August 2025) for the maintenance treatment of uncontrolled COPD with raised blood eosinophils, and is included in the final scope of this appraisal. Modelling dupilumab at this stage allows early consideration of its potential economic impact and supports alignment with evolving treatment pathways. A cost-comparison (CC) against dupilumab is also provided given that the MAIC showed numerical trends favouring mepolizumab for various exacerbation outcomes, with no statistically significant differences across exacerbation and HRQoL outcomes, indicating at least similar or greater health benefit. GSK believes that a CC against dupilumab would be appropriate, should dupilumab receive positive NICE guidance.

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3.3 Clinical parameters and variables

Clinical inputs required for the economic model include those related to baseline characteristics, exacerbation rates, responder rates and discontinuation rates for mepolizumab and dupilumab. The studies included in the analysis for each parameter are highlighted in Table 46.

For baseline characteristics and baseline exacerbation rates, the pooled trial analysis including the mITT-300 population of the mepolizumab trials (MATINEE, METREX, and METREO) and the IMPACT (183), and ECLIPSE (184) studies was utilised. IMPACT (183), and ECLIPSE (184) were included to increase sample size for estimating exacerbation rates among patients on background therapy and did not include mepolizumab. More detail on these trials is provided in Appendix J. Data included from the METREX (23, 24) and METREO (23, 25) trials was limited to participants with the eosinophilic phenotype of COPD and a mepolizumab dosage of 100 mg SC Q4W.

For treatment effect estimates, responder rates, and 52-week discontinuation rates associated with mepolizumab, the pooled mITT-300 data was used (MATINEE, METREX, and METREO). MATINEE had a study duration of up to 104 weeks, compared with 52 weeks for METREX and METREO. Therefore, discontinuation data after the first year in the model was taken from the 52-104 week period of the MATINEE study (21, 22).

For dupilumab, a MAIC was utilised in the absence of head-to-head data (Section 2.10). IPD from the pooled mITT-300 analysis were weighted to match the aggregate baseline characteristics of patients in the published pooled analysis of the dupilumab trials (BOREAS (168, 169) and NOTUS(170, 171)). The relative risk of the annualised rates of moderate/severe exacerbations and severe exacerbations from the MAIC were used to inform the treatment effect of dupilumab compared to mepolizumab in the model. Responder rates and discontinuation for dupilumab were estimated from inputs reported as part of the dupilumab NICE submission (20), with assumptions made where data was redacted or not available.

Table 46: Clinical inputs available by study

Parameters	Studies included in the analysis
Baseline characteristics	MATINEE, METREX, METREO, ECLIPSE, IMPACT [†]
Responder rates (mepolizumab)	MATINEE, METREX, METREO [†]
SoC exacerbation rates at baseline	MATINEE, METREX, METREO, ECLIPSE, IMPACT [†]
SoC exacerbation rates (subsequent exacerbations)	MATINEE, METREX, METREO, ECLIPSE, IMPACT [†]
Treatment effect (mepolizumab)	MATINEE, METREX, METREO [†]

Parameters	Studies included in the analysis
Discontinuation from mepolizumab treatment (1 st year)	MATINEE, METREX, METREO [†]
Discontinuation from mepolizumab treatment (year 2+)	MATINEE

Abbreviations: SoC, Standard of Care.

[†]The mITT-300 population of the MATINEE, METREX, and METREO trials is used

3.3.1 Patient characteristics

The patient baseline characteristics used as inputs in the CEM are taken from the pooled trial analysis including the mITT-300 population of the mepolizumab studies (MATINEE, METREX, METREO), and the IMPACT, and ECLIPSE studies, and are outlined in Table 47. The mean age of 65.4 years aligns well with real-world evidence (RWE) in patients with COPD across Europe (66 years) (189) and the mean age from the pooled BOREAS and NOTUS studies (65.1 years) (20). The majority of patients were male (69.0%) and had either moderate or severe COPD, with a small proportion (12.8%) categorised as having 'Very Severe' COPD. Baseline characteristics for the pooled mITT-300 population and the MATINEE only population are reported in Section 2.3.2.

Table 47: Population baseline characteristics used in the economic model

Population characteristic	Value used in CEM
Mean age (years)	65.4
Sex (% female)	31.0
COPD Severity by FEV ₁ %predicted	
Moderate: ≥50%–≤80% predicted	46.7
Severe: ≥30%–<50% predicted	40.4
Very Severe: <30% predicted	12.8

Source: Data on File (26)

Abbreviations: CEM, Cost-effectiveness model; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second.

3.3.2 Responder rates

A stopping rule is included in the model at 52-weeks, whereby only patients who are considered responders to treatment remain on mepolizumab. Responders are defined as patients that experience either:

- Fewer severe exacerbations than the year prior
- An equal number of severe exacerbations, and no increase in moderate exacerbations than the year prior.

This is aligned with the responder criteria used in the base case of the dupilumab submission (20).

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The proportion of patients achieving response in the pooled mITT-300 population and continuing treatment with mepolizumab at 52-weeks is shown in Table 48 for each health state. The proportion of patients receiving mepolizumab who do not respond to treatment are assumed to discontinue mepolizumab after 52-weeks and receive background therapy only in the CEM, with the corresponding costs and clinical outcomes applied.

For dupilumab, the proportion of responders by exacerbation health state was not reported in the NICE submission documents. The overall response rate amongst patients who received dupilumab plus background therapy at 52 weeks was 94.2%. To estimate the percentage of dupilumab patients who qualify as responders in each health state, a proportional increase relative to mepolizumab was estimated by comparing the net proportion of responders for mepolizumab to dupilumab (██████ to 94.2%, respectively, equivalent to ██████████); the resulting percentage increase was applied to each health-state responder percentage for mepolizumab to estimate the health-state specific response rate for dupilumab. The results of the adjusted response estimates for the dupilumab arm are presented below in Table 48 alongside the mepolizumab estimates. Note that this is a simplifying approach which does not account for between trial differences in populations which could impact the difference in the proportion of patient responding between trials.

Table 48: Proportion of responders to mepolizumab and dupilumab used in the CEM

Health state	No. of evaluable patients in each health state (out of mepolizumab population from pooled mITT-300)*	No. of patients meeting response criteria - mepolizumab (%)	Proportion meeting response criteria – dupilumab (%)
No exacerbations (baseline)	██████	██████	██████
One or more moderate exacerbations (no severe)	██████	██████	██████
Any moderate and 1 severe exacerbation [†]	██████	██████	██████
Any moderate and 2 or more severe exacerbations [‡]	██████	██████	██████

[†] This informs the 'severe exacerbation' and 'post severe exacerbation' states in the model [‡]This informs the 'frequent severe exacerbation' states in the model. *Meaning those on treatment at 52 weeks. ██████████

Abbreviations: CEM, Cost-effectiveness model; mITT, modified-intention-to-treat; ITT, intention-to-treat.

3.3.3 Exacerbation rates

3.3.3.1 Baseline exacerbation rates

Disease progression in the model was captured by the rate of moderate and severe exacerbations. The rate of first exacerbation (moderate or severe) as well as all subsequent exacerbations for background therapy were derived from the pooled COPD trials (MATINEE,

METREX, METREO, ECLIPSE, and IMPACT) in line with the source used for baseline characteristics in the model.

Baseline exacerbation rates are presented in Table 49 and Table 50 for the base-case and scenario analysis, respectively. Scenario analyses were performed with higher first exacerbation rates to evaluate the impact of potentially low exacerbation rates in clinical trials compared with real-world practice. The first scenario analysis involved calibrating the risk of first exacerbation to achieve a projected exacerbation rate within the first year of the model equal to the reported rate 12 months prior to randomisation in the MATINEE trial. A further scenario was performed in which rates were estimated from the post-randomization period in the METREX and METREO trials.

Table 49: Baseline exacerbation rates used in the model (base case)

Exacerbation type	Rate of first moderate exacerbation (95% CI)	Rate of first severe exacerbation (95% CI)
Pooled trial analysis post-randomization period	0.92 (0.85, 0.99)	0.17 (0.14, 0.20)

Abbreviations: CI, Confidence interval.

Table 50: Baseline exacerbation rates used in the model (scenario analysis)

Exacerbation type	Rate of first moderate exacerbation (95% CI)	Rate of first severe exacerbation (95% CI)
Scenario 1: Calibrated rate to achieve first-year model prediction equal to the rate in the year prior to randomization in MATINEE	1.58 (1.51, 1.66)	0.29 (0.25, 0.34)
Scenario 2: METREX/METREO post-randomization period	1.43 (1.19, 1.68)	0.20 (0.10, 0.29)

Abbreviations: CI, Confidence interval.

The rates of moderate and severe exacerbations in subsequent exacerbation health states for background therapy were estimated by applying rate ratios (RR) to the baseline moderate and severe exacerbation rates (Table 51). This is to reflect the increased risk of exacerbations following an exacerbation (246). RRs are estimated relative to the 'no exacerbation' health state and were derived from the pooled COPD trials (MATINEE, METREX, METREO, ECLIPSE, and IMPACT).

Table 51: RRs for subsequent exacerbations

Health State	RR of subsequent moderate exacerbation (95% CI)	RR of subsequent severe exacerbation (95% CI)
No exacerbations	Reference	Reference
Moderate exacerbations (0–3 months)		
Moderate exacerbations (>3 months)		
Severe exacerbations (0–3 months)		
Severe exacerbations (3–6 months)		
Severe exacerbations (6–9 months)		

Company evidence submission for mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237]

Health State	RR of subsequent moderate exacerbation (95% CI)	RR of subsequent severe exacerbation (95% CI)
Severe exacerbations (9–12 months)		
Frequent severe exacerbations (0–3 months)		
Frequent severe exacerbations (3–6 months)		
Frequent severe exacerbations (6–9 months)		
Frequent severe exacerbations (9–12 months)		
Post severe exacerbations (>12 months)		

Abbreviations: CI, Confidence interval; RR, rate ratio.

All estimates of the annual exacerbation rate were adjusted to quarterly rates and then transformed to provide probabilities of experiencing moderate or severe exacerbations per model cycle.

3.3.3.2 Exacerbation rate treatment effect (Year 1)

Rates of moderate and severe exacerbations were estimated for mepolizumab and dupilumab in the model. For mepolizumab, RRs for moderate and severe exacerbations in Year 1, derived from the pooled mITT-300 trials, were applied to baseline exacerbation rates, before calculating the cycle specific transition probabilities. In the pooled mITT-300 trials, mepolizumab was associated with a statistically significant decrease in the rate of moderate exacerbations () and a strong numerical decrease in the rate of severe exacerbations () compared with background therapy (Table 52).

Scenario analyses were considered where alternative RRs were assumed for mepolizumab. The first scenario utilises the MATINEE trial data in isolation to predict the treatment effect for mepolizumab. An additional treatment effect scenario was conducted in which reductions in first and subsequent exacerbations were considered separately, assuming that the treatment effect on reducing subsequent exacerbations is the same as that of the first exacerbation. This is considered to be an optimistic scenario given that the estimate of reductions in first exacerbations is numerically larger than that of the base-case analysis (not splitting by first and subsequent exacerbations), with mepolizumab associated with a statistically significant decrease in the rate of first moderate exacerbations of () and () in the rate of first severe exacerbations compared with background therapy.

The RRs for the base-case and scenario analyses are presented in Table 52 and Table 53 respectively.

Table 52: Treatment effect for exacerbation rates, mepolizumab vs. background therapy (base case)

Exacerbation type	Rate for moderate exacerbation (95% CI)	Rate for severe exacerbation (95% CI)
Base case: Pooled mITT-300 population		

Abbreviations: CI, Confidence interval; mITT-300, modified intention-to-treat 300 (participants with BEC ≥ 300 cells/ μ L at screening who received ≥ 1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline.

Table 53: Treatment effect for exacerbation rates, mepolizumab vs. background therapy (scenario analyses)

Exacerbation type	Rate for moderate exacerbation (95% CI)	Rate for severe exacerbation (95% CI)
Scenario 1: MATINEE only	0.79 (0.65, 0.96)	0.66 (0.43, 1.01)
Scenario 2: pooled mITT-300, subsequent exacerbations assumed equal to first exacerbations		
First exacerbation		
Subsequent exacerbations		

Abbreviations: CI, Confidence interval; mITT-300, mITT-300, modified intention-to-treat 300 (participants with BEC ≥ 300 cells/ μ L at screening who received ≥ 1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline.

For dupilumab, RRs informed by the MAIC (outlined in Section 2.10) were applied to mepolizumab exacerbation rates for moderate and severe exacerbations.

The risk of severe exacerbation for dupilumab + SoC is calculated by direct application of the between-biologic rate-ratio for severe exacerbation to the mepolizumab severe exacerbation rate.

As only RRs for moderate/severe exacerbations and severe exacerbations were estimated in the MAIC (Table 54), moderate exacerbations in each cycle for dupilumab were estimated as:

- The total exacerbation risk for dupilumab (i.e. applying the rate-ratio for total exacerbation risk for dupilumab vs. mepolizumab, to the total exacerbation risk for mepolizumab [estimated by the sum of the estimates for the risk of moderate exacerbation and the risk of severe exacerbation]),
- minus the directly estimated risk for a severe exacerbation.

Table 54: Treatment effect for exacerbation rates, mepolizumab vs. dupilumab

Exacerbation type	RR for moderate/severe exacerbation (95% CI)	RR for severe exacerbation (95% CI)
Mepolizumab vs. dupilumab	0.91 (0.60, 1.37)	0.68 (0.27, 1.72)

Abbreviations: CI, confidence interval; RR, rate ratio.

The MAIC analysis where CB is defined using investigator assessment is used in the base-case analysis. The rationale for this is that:

Company evidence submission for mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237]

- The definition used in the BOREAS and NOTUS trials which inform the MAIC analysis was based on study investigation of patient symptoms rather than patient self-report through the SGRQ. Therefore, this was considered more closely aligned with the investigator assessment in the MATINEE trial.
- In the restricted population from the mepolizumab trials, after applying the BOREAS/ NOTUS inclusion criteria in the MAIC, higher mean SGRQ scores at baseline were observed than that in the BOREAS/ NOTUS trials, regardless of the CB definitions. However, this difference was more aligned when CB was defined based on the investigator assessment compared to the SGRQ approach.(245)

A scenario analysis was performed in the model using the MAIC analysis where CB was determined based on responses to the SGRQ.

3.3.3.3 Exacerbation rate treatment effect (responders)

As outlined in Section 3.3.2, only patients who are judged to have responded to treatment, continue receiving mepolizumab or dupilumab past 52 weeks, in line with the stopping rule implemented in the dupilumab NICE submission (20). The number of patients meeting the criteria for response under the modelled stopping rule definition is presented in Section 3.3.2.

From Year 2 onwards, RRs of moderate and severe exacerbations for responders vs. baseline are used in the model (estimated at 52 weeks). These are presented in Table 55 for the pooled mITT-300 population. Mepolizumab is associated with a statistically significant decrease in the rate of moderate exacerbations (RR: [REDACTED]) and the rate of severe exacerbations (RR: [REDACTED]) compared with background therapy.

Table 55: RRs for exacerbations; responders (pooled mITT-300 population)

Health state	RR of moderate exacerbation; responders (95% CI)	RR of severe exacerbation; responders (95% CI)
Mepolizumab	[REDACTED]	[REDACTED]

Abbreviations: CI, confidence interval; mITT-300, modified intention-to-treat 300 (participants with BEC ≥ 300 cells/ μ L at screening who received ≥ 1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline; RR; rate ratio.

The treatment effect for responders is assumed to be the same in each moderate exacerbation state (0-3 months and ≥ 3 months) and severe exacerbation state (all severe/ frequent-severe timing states), as observations were not considered sufficient to produce estimates in each individual health state.

A scenario was included whereby RRs for exacerbations for responders were taken from MATINEE only (Table 56).

Table 56: RRs for exacerbations; responders (MATINEE only)

Health state	RR of moderate exacerbation; responders (95% CI)	RR of severe exacerbation; responders (95% CI)
Mepolizumab		

Abbreviations: CI, confidence interval; RR; rate ratio.

For dupilumab, the approach is aligned with that outlined in Section 3.3.3.2, where the RRs from the MAIC are applied to the mepolizumab responder exacerbation rates, and adjusted to estimate three-monthly probabilities for moderate, and severe exacerbations. This is a necessary approach given that the responder RRs from the dupilumab submission are redacted. There is however uncertainty in this approach, as the MAIC is aligned with the dupilumab trial data, and applied to responder rates derived based on the mepolizumab trial population, which is a different and broader population.

3.3.4 Treatment discontinuation

Alongside the proportion of patients achieving response, treatment discontinuation was captured in the model for mepolizumab and dupilumab. Pooled mITT-300 trial data is used in the base case to estimate 3-month probabilities of discontinuation for mepolizumab for the first year (Table 57).

For dupilumab, a 9.3% discontinuation probability in the first year was assumed in line with the probability reported in the dupilumab committee papers based on observed 52-week discontinuation in the pooled BOREAS and NOTUS trials(20). This was converted to a 2.41% probability of discontinuation in each three-month cycle in the model.

Table 57: Probability of discontinuation in Year 1, mepolizumab

Time period	Total number of patients on mepolizumab	Number of patients who discontinue mepolizumab	Probability of mepolizumab discontinuation
0–3 months			
4–6 months			
7–9 months			
10–12 months			

Source: Data on File (pooled mITT-300 analysis) (27)

Of the mepolizumab trials, only MATINEE included follow-up beyond 12 months. Therefore, the annualised discontinuation rate observed over the second year of the MATINEE trial for responders was converted to a probability of discontinuation per cycle and used in the model from Year 2 onwards for mepolizumab (Table 58). The discontinuation rate was also adjusted for patient years of follow-up in the trial, as total follow-up fluctuated between patients. This probability was also assumed for dupilumab in the base case.

Table 58: Probability of discontinuation in Year 2+

	Probability of mepolizumab discontinuation (SE)
Annual discontinuation rate from MATINEE trial	██████████
Probability of discontinuation per cycle	██████

Source: Data on File. MATINEE trial (21)

Abbreviations: SE, Standard error.

Alternative rates of discontinuation are considered in scenario analyses for year 2 onwards. A 15% annual discontinuation rate was used in the dupilumab NICE Company submission based on RWE from an asthma study and clinical expert opinion to the Company (20, 250-252). This is used for mepolizumab and dupilumab in scenario analysis and translates to a per cycle probability of discontinuation of 3.68%. This is considered a conservative estimate, given that the Company provided a range of estimates from the real-world between 15% and 25.8%. For completeness, a scenario analysis is performed where the █████% per cycle from MATINEE and 15% annual discontinuation rate from the dupilumab submission is assumed for mepolizumab and dupilumab for Year 2 onwards in the model.

It was assumed that the discontinuation probabilities do not differ by health state and remain constant for the remainder of the model time horizon. Once patients discontinue from mepolizumab or dupilumab treatment, they return to background therapy and are assigned the corresponding event risks and costs for the remainder of the model time horizon.

3.3.5 Mortality

Mortality in patients diagnosed with COPD is reported to be substantially higher than the general population, as discussed in Section 1.4.2. COPD exacerbations also increase the risk of mortality, with national data from OHID showing that approximately 4–5% of patients admitted to hospital for a COPD exacerbation die during their admission, and a further 9–11% die within 30 days of discharge (17). Severe exacerbations in particular, are associated with heightened risk of subsequent exacerbations and are a leading cause of mortality for patients with COPD (15).

Probabilities of death in each health state are therefore calculated based on three components:

- Background mortality for patients, excluding the impact of COPD
- A standardised mortality ratio (SMR), reflecting the increased probability of death for patients with COPD, excluding the impact of severe exacerbations
- A case-fatality rate for severe exacerbations.

Company evidence submission for mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237]

This is captured in the model to estimate mortality in each health state and is aligned with the approach taken in the dupilumab NICE submission (20).

3.3.5.1 Background mortality

General population mortality was collected from national life tables for England and Wales (2018–2020) (253). This dataset was chosen to avoid excess deaths in the general population due to the COVID-19 pandemic which may exist in more recent publications. COPD is a leading cause of death in the UK. The age-standardised mortality rate for COPD in England was 47.3 deaths per 100,000 population in 2023, with a three-year rolling average of 43.9 deaths per 100,000 (2021 to 2023) (17). In order to ensure that mortality associated with COPD is not double counted in the model, the general population mortality data in the model is adjusted to remove death events associated with COPD (ICD-10 codes J40-J44) (254).

3.3.5.2 COPD-related mortality

A SMR, which reflects the increased probability of death for patients with COPD vs. the general population, was applied to estimates of background mortality to calculate the probability of death for patients with severe COPD. The application of a SMR is consistent with the approach taken in the roflumilast (45) and dupilumab NICE submissions (20). The SMR value (2.50) for the severe COPD state, which excludes “mortality risk associated with hospital-treated exacerbations,” was sourced from Samyshkin *et al.*, 2014 (255). This value is aligned with the source used in the roflumilast NICE submission (45) and is similar to the SMR reported for severe COPD patients (2.33) in Whittaker *et al.*, 2024 (104), which estimated all-cause mortality hazard ratios associated with COPD severity based on an English dataset and was used in the company base case for the dupilumab NICE submission (20).

A scenario analysis has been included where the SMR for COPD-related mortality is not applied in the model.

3.3.5.3 Excess mortality for severe exacerbations

Case-fatality rates (CFR) were applied in the model to represent the increased risk of mortality associated with severe exacerbations. This aligns with the Company and External Assessment Group (EAG) preferred approach at ACM2 in the dupilumab NICE submission (20). The CFR (15.6% [CI: 10.9%, 20.3%]) was sourced from Hoogendoorn *et al.*, 2011 in the base case (256), and applied in severe and frequent severe exacerbation (0–3 months) health states only, corresponding to the ‘critical period’ associated with mortality following a severe exacerbation. Hoogendoorn *et al.*, 2011 is a meta-analysis which considers the probability of mortality resulting from a severe exacerbation across six studies.

An age-adjustment is also modelled from Hoogendoorn, using a 1.041 relative risk for each unit increase in age (years). It was assumed that mortality risk returns to that of the background mortality estimates after 3 months for patients with COPD following severe exacerbations.

The CFR has been tested in scenario analysis, using the 14.2% value reported in the NRAP clinical outcomes (2021-23) and outliers summary report (39), and is varied in the one-way sensitivity analysis (OWSA) to explore uncertainty around this parameter.

3.4 Measurement and valuation of health effects

3.4.1 Health-related quality of life data from clinical trials

EQ-5D-3L data collected in MATINEE was pooled along with EQ-5D-5L data collected in the METREX, METREO, and IMPACT studies (cross-walked to EQ-5D-3L where needed, see Section 3.4.2) to estimate HSUVs. The pooled utility estimates were used both for the baseline utility and disutilities associated with health states.

Table 59 reports the results of the pooled utility analyses as well as the number of records available for informing the EQ-5D data within the model, across the four studies mentioned, by health state. The number of records available for the more severe states were less common.

Table 59: Assessment of EQ-5D and data collected in proximity to exacerbation events

Exacerbation parameter	Number of EQ5D records	EQ-5D (SE)
Baseline utility		
No exacerbations	████	██████████
Disutilities		
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)	████	██████████

Abbreviations: SE, standard error.

3.4.2 Mapping

Currently, there is no approved value set for the EQ-5D-5L in England. Therefore where EQ-5D-5L were collected in certain trials, these were mapped to EQ-5D-3L (199) using the cross-walk approach by Hernández Alava M, Pudney S. (2017) as recommended in NICE guidelines (2022) (198, 199).

3.4.3 Health-related quality of life studies

An SLR was conducted on 12th October, 2016, and updated on 11th May 2018, 24th July 2024, and 14th August 2025 to identify HRQoL/utility data in patients with moderate to very severe COPD. A detailed description of the SLR methods, full results and quality assessment of the identified economic evaluations is presented in Appendix F.

Of the 90 included studies in the SLR, 85 were primary studies that assessed indirect and direct utility measures, and five involved mapping approaches (four empirical mapping studies (Starkie 2011, Boland 2015, Evans 2018, Lim 2019) that developed or validated algorithms to estimate EQ-5D utilities, and one model application (NICE 2018/2019), which applied an existing mapping algorithm within an economic model). Summary data for all included studies is provided in Appendix F. Of the 85 included primary studies, 22 (19, 257-277) met the NICE reference case requirements for HSUV evidence, in that:

- they reported utility values derived from a representative UK population or using UK tariffs,
- and were elicited using a preference-based measure, such as time trade-off (TTO) or standard gamble, and an appropriate method for valuing health states (Appendix F).

Within this NICE reference case aligned subset, seven studies (257, 258, 262-264, 269, 271) reported utilities for patients with COPD exacerbations.

Among these seven exacerbation studies, five were observational or secondary analyses, one was a non-pharmacological interventional RCT (258), and one was a trial-based cost-utility analysis. Of these, four studies (258, 262, 263, 269) reported utility values for hospitalised patients with a moderate-to-severe exacerbation, including acute admission and short-term post-discharge periods. One study (271) reported utilities for general practice/outpatient-treated exacerbations, and two discrete-choice experiment (DCE) studies (257, 264) reported preference-based utilities for exacerbations requiring antibiotics/steroids (ambulatory) or hospital treatment.

Across the seven studies, participants were typically older adults (mean age 60–70 years) with a balanced sex distribution (40–55% female) and a history of moderate-to-very severe COPD.

Sample sizes ranged from 81 (271) to over 3,000 (263). Four studies (258, 262, 263, 269) used spirometric GOLD or FEV₁ criteria (generally GOLD II–IV), while three studies (257, 264, 271) relied on clinical or self-reported severity. No study stratified or reported results by BEC; severity was defined clinically or via spirometry.

Across the included evidence, utilities for COPD exacerbation health states were predominantly derived from EQ-5D instruments (3L or 5L) valued using UK tariffs, with additional evidence from discrete choice experiments (DCEs) providing patient-elicited preference weights. Most studies assessed hospitalised or ambulatory exacerbations among older adults (mean age 60–70 years) with moderate-to-very severe COPD and a history of exacerbations. Utilities were obtained through in-person or postal EQ-5D surveys in clinical settings, or online administration for DCEs. Reported EQ-5D utilities during hospitalised exacerbations typically ranged from 0.4–0.6, rising to around 0.7 for ambulatory events, corresponding to short-term disutilities of –0.06 to –0.16 depending on severity and recovery phase. The single non-pharmacological RCT (258) found no material difference between study arms, while DCEs (257, 264) demonstrated substantially larger preference decrements for hospital-treated vs. ambulatory exacerbations. Overall, the results across these studies are consistent, showing a temporary but clinically meaningful HRQoL decline during exacerbations.

A summary of the seven exacerbation studies is presented in Table 60 (full details are provided in Appendix F).

Table 60: Summary of studies reporting utilities for COPD exacerbation health states (NICE reference-case aligned subset)

Study (Year)	Design / Setting	Population characteristics	Valuation method	Health state assessed	Reported utility (mean [SD] or disutility)
O'Reilly <i>et al.</i> , 2007 (269) (UK)	Observational, hospital admission	n = 149; mean 69.9 y; 54 % female; GOLD 0–IV (39 % III, 34 % IV); mean FEV ₁ 41 %	EQ-5D (UK tariff; UK population)	Hospitalised AECOPD (acute + post-discharge)	Admission –0.08 (0.40); post-discharge 0.58 (0.32)
Paterson <i>et al.</i> , 2000 (271) (UK)	Observational, GP/outpatient	n = 81; mean 61 y; 53 % female; clinical diagnosis of chronic bronchitis	EQ-5D (UK tariff; UK population)	Ambulatory exacerbation (antibiotic/steroid treated)	0.71 (at visit); disutility –0.10 (moderate) to –0.16 (severe)
Cross <i>et al.</i> , 2012 (258) (UK)	RCT (non-pharmacological; manual chest physiotherapy vs. control), hospital	n = 522; mean 69 y; 42–45 % female	EQ-5D (UK tariff)	In-hospital and 6-month post-AECOPD	Hospital 0.43–0.45; 6 months 0.45–0.48 (no difference between arms)
Hall <i>et al.</i> , 2025 (262) (UK)	Trial-based cost-utility analysis (COPDPredict™); NHS setting	n = 80; mean ≈ 65 y; GOLD B/D (≥ 85 % GOLD D)	EQ-5D-5L (UK cross-walk tariff)	Hospitalised exacerbation (disutility per quarter)	–0.06 per 3 months; EQ-5D 0.53 to 0.59 (intervention) vs. 0.49 to 0.49 (control)
Jackson <i>et al.</i> , 2024 (263) (UK)	Observational (post-hoc ETHOS trial analysis)	n = 3,316; mean 64.7 y; 40 % female; FEV ₁ 25–65 %; ≥ 1 prior AE	EQ-5D-5L (MMRM model)	Current and previous moderate/severe AE	Moderate AE –0.055; severe AE –0.090; prior AE –0.014 (moderate)/ –0.024 (severe)
Cook <i>et al.</i> , 2022 (257) (Multi-country)	Cross-sectional survey (DCE) – UK subset	n = 1,050; mean 60.5 y; 49 % female; self-reported moderate (54 %) or severe (35 %)	DCE (hierarchical Bayesian effects-coding)	Flare-ups requiring antibiotics/steroids or hospital care	Ambulatory +0.15; hospital –0.88 (preference weights)
Jones <i>et al.</i> , 2024 (264) (Multi-country)	Cross-sectional survey (DCE) – UK subset	n = 1,050; self-perceived mild–very severe COPD	DCE (econometric model)	Acute exacerbation requiring antibiotics/steroids vs. hospital stay	Ambulatory +0.154; hospital 0 (reference)

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; CAT, COPD Assessment Test; CASA-Q, Cough and Sputum Assessment Questionnaire; COPD, chronic obstructive pulmonary disease; DCE, discrete choice experiment; EQ-5D, EuroQol 5-Dimension; EQ-5D-5L, EuroQol 5-Dimension 5-Level; FEV₁, forced expiratory volume in one second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HRQoL, health-related quality of life; HSUV, health-state utility value; MMRM, mixed model for repeated measures; MCP, manual chest physiotherapy; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; RCT, randomised controlled trial; SD, standard deviation; UK, United Kingdom.

Company evidence submission for mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237]

Of the five studies involving mapping approaches (19, 278-281), these have developed or applied mapping methods to estimate EQ-5D utilities in COPD. Starkie *et al.*, (2011) (281) developed the widely adopted SGRQ to EQ-5D equation using UK value sets, providing the reference algorithm now applied in most health economic analyses. Building on this, the NICE (2018/2019) (19) COPD economic model implemented the Starkie function within its framework, converting published SGRQ data to EQ-5D utilities by GOLD stage for use in the national cost-effectiveness model. Evans *et al.*, (2018) (279) further validated the Starkie algorithm longitudinally using patient-level data from the RENEW and NETT trials, generating new mapped EQ-5D utilities and QALY estimates for endobronchial coil therapy. Complementary work by Boland *et al.*, (2015) (278) compared alternative regression specifications across Dutch COPD trials, confirming ordinal least squares (OLS) regression models as the most reliable for predicting EQ-5D, particularly at lower utility values, while Lim *et al.*, (2019) (280) extended mapping methods to the CAT questionnaire, testing OLS, generalised linear model (GLM), Tobit, and beta regression approaches.

Table 61: Summary of included studies that have developed or applied mapping methods to estimate EQ-5D utilities in COPD

Study (Year)	Population description	Mapping approach / Algorithm
Starkie <i>et al.</i> , 2011 (281)	Patients with moderate-to-very severe COPD enrolled in the TORCH trial (salmeterol/fluticasone, salmeterol, or placebo arms); EQ-5D utilities valued using the UK general population tariff.	Developed the reference SGRQ → EQ-5D mapping equation: $EQ-5D = 0.9617 + 0.0013 \times SGRQ \text{ Total} + 0.0001 \times (SGRQ \text{ Total})^2 + 0.0231 \times \text{Male}$. Widely validated and later implemented in NICE analyses as the standard algorithm for converting SGRQ scores to EQ-5D utilities.
Boland <i>et al.</i> , 2015 (278)	Pooled data from three Dutch COPD trials (RECODE, GO-AHEAD, and MARCH) including mild-to-very severe and post-exacerbation patients.	Compared alternative regression specifications (OLS, Tobit, GLM) to predict EQ-5D (Dutch tariff) from clinical and patient-reported data. The 10-parameter OLS model (GO-AHEAD dataset) achieved the lowest error (MAE, RMSE), performing best for $EQ-5D < 0.5$.
Evans <i>et al.</i> , 2018 (279)	Patients with severe emphysema from the RENEW and NETT trials.	Applied and validated the Starkie (2011) SGRQ → EQ-5D mapping using longitudinal patient-level data. Developed multilevel regression models to predict EQ-5D from clinical covariates (FEV ₁ , RV, 6MWD, treatment response), generating new mapped utilities and QALY estimates for coil therapy.
Lim <i>et al.</i> , 2019 (280)	Patients with COPD (FEV ₁ /FVC < 0.7) recruited from three tertiary hospitals in Korea.	Developed CAT to EQ-5D-3L mapping models using OLS, GLM, Tobit, and beta regressions. Best-fit models incorporated total CAT score (and its square), age, and sex, e.g., $EQ-5D = a + b_1 \times CAT + b_2 \times CAT^2 + c_1 \times Age + c_2 \times Sex$.
NICE 2018/2019 (19)	UK COPD population represented in the NICE NG115 (19) economic model.	Model application of the Starkie <i>et al.</i> , 2011 (281) algorithm within the NICE cost-effectiveness framework, converting SGRQ data from a published study Jones <i>et al.</i> , (2011) to EQ-5D utilities by GOLD stage. Used to generate stable health-state utilities

Study (Year)	Population description	Mapping approach / Algorithm
		consistent with the NICE reference case. Disutilities from Rutten van Molken (274)

Abbreviations: 6MWD, six-minute walk distance; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; EQ-5D, EuroQol 5-Dimension; EQ-5D-3L, EuroQol 5-Dimension three-level; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; GLM, generalised linear model; GOLD, Global Initiative for Chronic Obstructive Lung Disease; MAE, mean absolute error; NG115, NICE Guideline 115; NICE, National Institute for Health and Care Excellence; OLS, ordinary least squares; QALY, quality-adjusted life year; RECODE, Randomised Clinical Trial on Effectiveness of Integrated COPD Management in Primary Care; RENEW, Lung Volume Reduction Coil Treatment in Patients with Emphysema trial; RMSE, root mean square error; RV, residual volume; SGRQ, St George's Respiratory Questionnaire; TORCH, Towards a Revolution in COPD Health trial.

3.4.4 Adverse reactions

AEs are not explicitly modelled and therefore, disutilities for AEs are not required. AE type and frequency are assumed not to be significantly different between treatments in the model and would therefore not impact the incremental outcomes. In addition, discontinuation rates are assumed to capture potential treatment-related discontinuation.

3.4.5 Health-related quality of life data used in the cost-effectiveness analysis

Table 62 summarises the utility values used in the base case.

Age-adjusted utilities were applied to reflect decreases in HRQoL seen in the general population and to ensure that utilities did not exceed general population values at a given age. Utility decrements associated with age were derived using the expected EQ-5D-3L values published by Hernández Alava, Pudney and Wailoo, 2022 (282). A scenario has been included where age-adjustment is not implemented in the model.

The utilities were assessed for their face validity, in terms of values across health states following an intuitive ordering (more severe health states having a higher disutility). Based on this, a scenario was undertaken capping the value for disutility in the post-severe (>12 months) state by setting it equal to the severe (9–12 months) state.

Table 62: Summary of utility values for cost-effectiveness analysis

State	Utility/disutility value: mean (SE)	95% CI	Reference in submission (section and page number)	Justification
No exacerbations	████	██████████	Section 3.4.1	Utilities have been taken from an analysis pooling EQ-5D across MATINEE, METREX, METREO,
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)	████	██████████		

Company evidence submission for mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237]

State	Utility/disutility value: mean (SE)	95% CI	Reference in submission (section and page number)	Justification
Frequent severe (0–3 months)	████	██████████		and IMPACT studies
Frequent severe (3–6 months)	████	██████████		
Frequent severe (6–9 months)	████	██████████		
Frequent severe (9–12 months)	████	██████████		

Source: Pooled analyses of MATINEE, METREX, METREO, and IMPACT studies (26).
Abbreviations: CI, confidence interval; SE, standard error.

Scenarios were also undertaken using alternative sources for disutility values.

Jackson *et al.*, 2024 (263) utilised data from the ETHOS study to estimate the disutility associated with exacerbations in moderate to very severe COPD patients. Disutilities were separated by recent exacerbation and the additional ongoing disutility associated with previous exacerbations was estimated. Jackson *et al.*, was considered as a source by the EAG in the dupilumab submission, however, was not pursued due to the values only being available using EQ-5D-5L.

An alternative scenario is provided using the EAG and Committee preferred values from the roflumilast NICE (TA461) (45) submission base case (Hoogendoorn *et al.*, 2011 (283)). Values were reported for the disutility associated with moderate (–0.0166) and severe (–0.0482) exacerbations and it was assumed that the utility value would have returned to normal after 4.5 months. Therefore, the disutility three months after an exacerbation in the model was assumed to be zero. Although Hoogendoorn *et al.*, 2011 (284) was identified in the SLR, it did not meet the criteria for inclusion in the NICE reference-case subset, as utilities were not derived using UK tariffs. However, these values have been explored for use in previous NICE technology appraisals (including TA761 for roflumilast (45) and in the dupilumab submission (20)) to inform exacerbation disutility assumptions. This scenario was therefore included to maintain consistency with prior NICE appraisals and to test sensitivity to alternative, previously explored sources of exacerbation disutility. It was also tested by the EAG in the dupilumab NICE submission (20) alongside the roflumilast committee preferred baseline utility value

██

A scenario analysis has been performed in which individual SGRQ scores from the pooled trial analysis including the mITT-300 population of the mepolizumab studies (MATINEE, METREX, METREO), and the IMPACT, and ECLIPSE studies, were converted to EQ-5D weights using the formula derived by Starkie *et al.*, 2011 (281).

Company evidence submission for mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237]

The disutility values applied in the model for these scenarios are presented in Table 63.

Table 63: Summary of disutility values for cost-effectiveness analysis: scenario analyses

State	Mean disutility values: Jackson <i>et al.</i> , 2024 (Scenario 1)	Mean disutility values: Hoogendoorn <i>et al.</i> , 2011 (Scenario 2)	Mean disutility values: SGRQ converted to EQ-5D (Scenario 3)
Moderate (0–3 months)	–0.055	–0.0166	██████
Post-moderate	–0.014	0	██████
Severe (0–3 months)	–0.090	–0.0482	██████
Severe (3–6 months)	–0.024	0	██████
Severe (6–9 months)	–0.024	0	██████
Severe (9–12 months)	–0.024	0	██████
Post-severe (>12 months)	–0.024	0	██████
Frequent severe (0–3 months)	–0.090	–0.0482 [†]	██████
Frequent severe (3–6 months)	–0.024	0	██████
Frequent severe (6–9 months)	–0.024	0	██████
Frequent severe (9–12 months)	–0.024	0	██████

Source: Jackson *et al.*, 2024 (263)

[†]Assumed equal to first severe exacerbation disutility

Abbreviations: EQ-5D, EuroQol five dimension; SE, standard error; SGRQ, St Georges Respiratory Questionnaire.

3.5 Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted on 14th October 2016 and 17th May 2018, and subsequently updated on 25th July 2024, and 24 August 2025 to identify economic evaluations (cost-effectiveness studies [Section 3.1 and Appendix E] and/or HCRU and costs studies [Appendix G]) in patients with moderate, severe or very severe COPD treated with triple therapy (ICS/LABA+LAMA) or dual therapy with add on therapies. Of the included studies, 25 (19, 45, 141-144, 152, 219, 220, 262, 285-299) were conducted in a UK setting. A detailed summary of the identified UK-based HCRU and cost studies is provided in Appendix G.

3.5.1 Intervention and comparators' cost and resource use

3.5.1.1 Treatment acquisition costs

Treatment acquisition costs were calculated using treatment prices and the respective dosing schedules, sourced from GlobalData Pharmaceutical Prices (POLI), which uses prices of drugs from the UK's Dictionary of Medicines and Devices, aligned with the source used by the BNF (300). For mepolizumab, a confidential Patient Access Scheme (PAS) discount of ██████% is in place, resulting in a net price of £██████ per 100 mg per 1ml solution. Dupilumab has a confidential PAS in place, therefore list price is used.

Company evidence submission for mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237]

Dosing schedules were aligned with SmPC for each treatment. Treatment costs in each cycle for mepolizumab and dupilumab, are estimated, with patients who discontinue treatment receiving background therapy only, as described in Section 3.3.4.

Background therapy consists of a basket of inhaler treatments, weighted by proportions outlined in Section 3.2.3.1.

Treatment acquisition costs are summarised in Table 64.

Table 64: Drug acquisition costs for intervention and comparator treatments

Intervention	Pack size (mg)	Number of units	Price per pack	Dose per admin (mg)	Cost per model cycle
Mepolizumab	100	1	List price: £840.00 PAS price: £[REDACTED]	100 mg administered as a SC injection Q4W	£2,739.38 (List price) £[REDACTED] (PAS price)
Dupilumab	300	2	List price: £1,264.89	300mg administered as a SC injection Q2W	£4,125.01
Trelegy Ellipta(38.0% of background therapy)	Inhaler	30	£44.50	1 inhalation, QD	£135.45
Trimbow (59.4% of background therapy)		120	£44.50	2 inhalations, BID	
Trixeo aerosphere (2.6% of background therapy)		120	£44.50	2 inhalations BID	

Source: GlobalData (300).

Abbreviations: BID, twice daily; Q2W, every 2 weeks; Q4W, every 4 weeks; QD, once daily; PAS, patient access scheme; SC, subcutaneous.

3.5.1.2 Treatment administration costs

Background therapy consists of inhalers, which are self-administered.

It was assumed that mepolizumab and dupilumab would be self-administered in 95% of patients, in line with the expert feedback provided to the EAG in the dupilumab NICE submission, which assumed that 5% of dupilumab patients would receive administration support via a home nurse visit (20). For patients that self-administer, nurse training was assumed in the first cycle. A nurse home visit, and nurse training is assumed to take 1 hour of nurse time and cost £52 for each, based on the Personal Social Services Research Unit (PSSRU) cost for a band 5 hospital-based nurse, including qualifications (301).

3.5.2 Health-state unit costs and resource use

The model assigns costs for routine follow-up care to each health-state. Additionally, costs associated with the exacerbation events themselves were assigned in the model cycle when the exacerbation was predicted.

Company evidence submission for mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237]

It is acknowledged that there is an elevated risk of CV events in people with COPD (10). However, given that few CV events were observed across the considered trials, with no meaningful difference between arms reported, and that CV events are unlikely to be a significant driver of model results, CV events were not modelled explicitly, which is likely to be a conservative assumption.

3.5.2.1 COPD management costs

Frequency of resource use for the management of COPD is assumed to be independent of health state and is based on the NICE NG115 COPD economic model report (19). As the values outlined in the NICE report are stratified by GOLD severity, the model first weights frequency by the proportion of patients in each GOLD severity group (outlined in Section 3.3.1), and then adjusts for the cycle length in the model (dividing by 4).

COPD management costs are summarised in Table 65.

Table 65: COPD management costs

Resources	Cost per unit (£)	Frequency per cycle	Source for cost
GP visit	45.00	0.34	Unit cost for a GP, Cost per surgery consultation lasting 10 mins (including qualifications and direct care staff costs); unit costs of health and social care (301)
Respiratory team visit	289.00	0.35	Episode assumed to comprise six 40-minute visits from either a band 6 (75%) or band 7 (25%) PSSRU 2023/24 hospital nurse (301)
Outpatient visit	204.98	0.18	NHS reference costs 2023/24 (249) – weighted average of Respiratory services, Outpatient attendances (340 and 341)
Spirometry	37.84	0.43	NHS Reference Costs 2010/2011, outpatient spirometry and bronchodilator response test – inflated to 2023/34 using the PSSRU inflation indices (20, 301)
Pulmonary rehabilitation	158.78	0.01	NHS Reference Costs 2023/24 (249) – weighted average of pulmonary rehabilitation service outpatient procedures
Oral corticosteroids	0.49	0.38	GlobalData 2025 (300)
Home oxygen therapy (proportion of patients)	19.33	0.02	Hertel <i>et al.</i> , 2012 (302) – inflated to 2023/24 using the PSSRU inflation indices
Influenza vaccine (proportion of patients)	13.50	0.18	GlobalData 2025 (300)
CT scan	102.84	0.01	NHS Reference Costs 2023/24 (249) – Directly accessed CT scans - Diagnostic Imaging Service, excluding 18 years and under (RD20A)
Total costs per model cycle (£)	176.16		

Abbreviations: COPD, chronic obstructive pulmonary disease; CT, computerised tomography; GP, general practitioner; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

3.5.2.2 Exacerbation event costs

3.5.2.2.1 Moderate exacerbations

Frequency of resource use for moderate exacerbations is based on the NICE NG115 COPD economic model report (19). Costs are applied per model moderate exacerbation event.

Moderate exacerbation resource costs are summarised in Table 66.

Table 66: Moderate exacerbation resource use costs

Resources	Cost per unit (£)	Frequency per event	Source for cost
A&E visit without admission	123.75	0.30	NHS reference costs 2023/24 (249) – Emergency Medicine, weighted average of Emergency Medicine, No investigation with No Significant Treatment (VB11Z)
Respiratory team visit	289.00	0.10	Episode assumed to comprise six 40-minute visits from either a band 6 (75%) or band 7 (25%) PSSRU 2023/24 (301)
GP Visit	45.00	1.00	Unit cost for a GP, Cost per surgery consultation lasting 10 mins (including qualifications and direct care staff costs) – unit costs of health and social care (301)
OCS (number of prescriptions)	0.49	0.00	GlobalData 2025 (300)
Antibiotics (number of prescriptions)	5.00	0.07	GlobalData 2025 (300)
Total costs per model cycle (£)	121.52		

Abbreviations: A&E, accident and emergency; GP, general practitioner; NHS, national health service; OCS, oral corticosteroids; PSSRU, personal social services research unit.

3.5.2.2.2 Severe exacerbations

Frequency of resource use for severe exacerbations is aligned with the proportions used in the dupilumab NICE submission (20), which were based on a utilisation analysis using the hospital episode statistics (HES) database over the period 2018–2024, where a severe exacerbation was defined as requiring a hospital stay. Follow-up outpatient appointments within 30 days were not costed in this analysis, in line with the EAG preferred base case in the dupilumab NICE submission, which removed this cost from the Company resource use estimates (20).

Costs are applied per severe exacerbation event in the model. In the absence of granular data, resource use frequencies and costs for frequent severe exacerbations in the model were assumed the same. This assumption is likely conservative, as evidence indicates that exacerbations contribute to disease progression, accelerated decline in lung function (12), and increased risk of mortality and subsequent exacerbations (54, 82, 105). As COPD severity

Company evidence submission for mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237]

increases, subsequent exacerbations are often more severe and resource intensive (11, 16), indicating that applying the same cost to all severe events may underestimate the actual economic burden.

Severe exacerbation resource costs are summarised in Table 67.

Table 67: Severe exacerbation resource use costs

Resources	Cost per unit (£)	Frequency per event	Source for cost
Ambulance transport	250.02	70.00%	NHS reference costs 2023/24 (249) – weighted average of ambulance codes
A&E admission	353.92	88.00%	NHS reference costs 2023/24 (249) – weighted average of Emergency Medicine, Category 1 Investigation with Category 3-4 treatment codes (VB06Z)
Hospital LOS	3,350.49	1 day	NHS Reference Costs 2023/24 (249) – weighted average of COPD nonelective long stay, excluding one day or less category
ICU LOS	2,436.67	1.00%	NHS Reference Costs 2023/24 (249) – weighted average of all non-specific, general adult critical care bed days
Readmission within 30 days	3,350.49	14.00%	Assumption, same as hospital stay (LOS)
Ventilation	1,071.02	7.00%	NHS Reference Costs 2023/24 (249) – nonelective, non-invasive ventilation, 19 years and over (short-stay and long-stay)
Oxygen therapy	309.05	2.00%	NHS Reference Costs 2023/24 (249) – nonelective oxygen assessment and monitoring (non-elective short stay)
CT scan	102.84	10.00%	NHS Reference Costs 2023/24 (249) – Directly accessed CT scans - Diagnostic Imaging Service, excluding 18 years and under (RD20A)
Echocardiogram	137.49	5.00%	NHS Reference Costs 2023/24 (249) – directly accessed simple echocardiograms, 19 years and over (Diagnostic Imaging Services)
CPAP therapy	1,071.02	1.00%	Assumption, same as ventilation
Follow-up outpatient appointments within 90 days of exacerbation	204.98	37.00%	NHS reference costs 2023/24 (249) – weighted average of Respiratory services, Outpatient attendances (340 and 341)
Total costs per model cycle (£)	4,515.26		

Abbreviations: A&E, accident and emergency; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; CT, computerised tomography; ICU, intensive care unit; LOS, length of stay; NHS, national health service.

3.5.3 Adverse reaction unit costs and resource use

AEs were not explicitly modelled in this analysis. Adverse event type and frequency are assumed not to be significantly different between arms in the model and would therefore not impact the incremental outcomes.

Company evidence submission for mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237]

3.5.4 Miscellaneous unit costs and resource use

Indirect costs are not modelled in the base-case analysis, however the cost associated with productivity loss and early retirement is explored in a scenario analysis. COPD is associated with increased risk of hospitalisation, comorbidities and death, as outlined in Section 1.4.3. and as such has been shown to be associated with productivity loss in patients of working age (303), and in some cases, early retirement (304).

Whilst caregiver burden has also been documented, caregiver costs were not considered in the model due to the lack of available cost data in England (43).

3.5.4.1 Productivity loss

Productivity days lost per month in the GOLD severity groups were sourced from Jansson *et al.*, 2013 (303) and weighted by the proportion of patients in each GOLD severity category from the pooled trial analysis (outlined in Section 3.2.1). Productivity days lost per model cycle (3 months) were then estimated.

Additional days lost due to exacerbations are estimated in the model. Half a day was assumed to be lost due to moderate exacerbations to account for a patient GP visit, and 5.25 days were assumed to be lost for severe and frequent severe exacerbations. Days lost due to moderate and severe exacerbations were multiplied by the mean number of moderate (■) and severe (■) exacerbations experienced the year prior to randomisation in the pooled trials, respectively.

A productivity loss cost was then estimated for patients under retirement age and employed, by estimating days lost per model cycle (303) and multiplying by the average salary per day in the UK (305). Early retirement was accounted for as outlined in Section 3.5.4.2. The proportion of patients under the retirement age in each model cycle was estimated by assuming a normal distribution around the mean retirement age. A summary of inputs used to estimate productivity loss in the model is provided in Table 68.

Table 68: Productivity loss model inputs

Parameter	Unit value	Source
Retirement age (years) (mean (SD))	66 (4)	ONS milestones (306)
Employment rate (%)	77.86	ONS A04: Summary of employment, unemployment and economic inactivity for people below state pension age 2025 (307)
Average annual salary (£)	37,430	ONS employee earnings in the UK 2024 (305)
Number of working days in a year	256	Assumption
Productivity days lost per cycle (baseline)	2.15	Jansson <i>et al.</i> , 2013 (303)

Parameter	Unit value	Source
Days lost per moderate exacerbation event	■	Half day multiplied by average moderate exacerbations year prior to randomisation (■), adjusted for 3-month model cycle length
Days lost per severe exacerbation event	■	5.25 days multiplied by average moderate exacerbations year prior to randomisation (■), adjusted for 3-month model cycle length

Abbreviations: ONS, Office for National Statistics; SD, standard deviation; UK, United Kingdom.

3.5.4.2 Early retirement

The proportion of patients retiring early due to COPD was estimated in Wacker *et al.*, 2016 (304) stratified by GOLD severity stage. These proportions are weighted by the proportion of patients in each GOLD severity category from the pooled trial analysis (outlined in Section 3.2.1) and multiplied by the number of days in each cycle, and the average salary per day (Section 3.5.4.1). No retirement loss is expected to occur as a result of exacerbation events, with the total cost being applied to each treatment, in each health state.

Inputs associated with early retirement are summarised in Table 69.

Table 69: Early retirement loss model inputs

Parameter	Unit value	Source
Weighted early retirement (%)	33.3	Wacker <i>et al.</i> , 2016 (304) and pooled trial analysis
Early retirement in the general population (%)	14.7	Wacker <i>et al.</i> , 2016
Excess early retirement for patients with COPD (%)	18.6	Calculated
Total cost per cycle for an early retirement (£)	1,736	

Abbreviations: COPD, chronic obstructive pulmonary disease.

3.6 Severity

The estimated QALY shortfall for the target population of patients with COPD treated with current SoC does not justify the application of a severity modifier.

3.7 Uncertainty

Previous models built in COPD have explicitly considered lung function decline alongside exacerbations (20, 45). Clinical expert advice to the Company sought throughout the model development process has confirmed that the model structure is appropriate and reduction in exacerbations is the most important determinant of health outcomes for this population. Furthermore, studies have shown that exacerbations are strong predictors of mortality, poorer quality of life, and increased future risk of exacerbations. Each event contributes to worsening disease severity and greater HCRU, including hospitalisations and emergency department

Company evidence submission for mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237]

visits (11, 15, 16, 54, 82). Therefore, it was not considered appropriate to model lung function decline. As a result, the inputs and assumptions included in the model are not all directly comparable to those used in the dupilumab NICE submission. Moreover, the dupilumab model was also based on data from the BOREAS/NOTUS trials, which had some differences in trial inclusion criteria compared to the mepolizumab trials. Nevertheless, assumptions have been included in order to attempt to facilitate a comparison with dupilumab populated by inputs from the MAIC and the NICE submission Committee papers (20). These assumptions have been outlined throughout this document and uncertainty has been explored in one-way and probabilistic sensitivity analysis (Section 3.11).

Mepolizumab was associated with a statistically significant decrease in the rate of moderate/severe exacerbations and a numerically favourable decrease in the rate of severe exacerbations compared with background therapy in the pooled mITT-300 population (Section 2.6.3), with consistent results observed across the individual trials. The pooled mITT-300 analysis allowed for an increased sample size in determining the treatment effect of mepolizumab, with [REDACTED] of patients experiencing 1 or more severe exacerbations across the trials. It is important to note that mepolizumab was associated with a statistically significant decrease in the rate of first severe exacerbations, with fewer observations recorded for subsequent severe exacerbation rates in the analysis. A large and statistically significant reduction in both moderate and severe exacerbations was also observed in mepolizumab responder patients in MATINEE and the pooled mITT-300 population. Scenario analysis has been performed around the rate of severe exacerbations for mepolizumab compared with background therapy.

The RRs associated with exacerbations, as well as disutility values, were derived in correspondence with each of the health states in the model. Consequently, data informing some health states (such as the frequent severe exacerbations health states) was based on fewer patients and hence is associated with additional parameter uncertainty.

Key parameters are tested within probabilistic sensitivity analysis, as well as deterministic sensitivity analyses.

3.8 Managed access proposal

Mepolizumab is not considered to be a candidate for a managed access scheme.

3.9 Summary of base-case analysis inputs and assumptions

3.9.1 Summary of base-case analysis inputs

A summary of variables applied in the economic model is provided in Table 70.

Company evidence submission for mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237]

Table 70: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Model settings			
Time Horizon	30 years	-	3.2.2.6
Discount rate costs and benefits	3.5%	-	3.2.2.6
Age (years)	65.4	-	3.3.1
Sex (% female)	31.0	-	3.3.1
COPD severity by FEV ₁ %predicted	Moderate: ≥50%–≤80% predicted: 46.7 Severe: ≥30%–<50% predicted: 40.4 Very Severe: <30% predicted: 12.8	-	3.3.1
Clinical inputs			
Proportion of responders to mepolizumab/ dupilumab	Table 48	Beta	3.3.2
Rate of first moderate exacerbation at baseline	0.92	0.85, 0.99 Normal	3.3.3.1
Rate of first severe exacerbation at baseline	0.17	0.14, 0.20 Normal	3.3.3.1
Rate of subsequent moderate exacerbations	Table 51	Normal	3.3.3.1
Rate of subsequent severe exacerbations	Table 51	Normal	3.3.3.1
Treatment effect for moderate exacerbations: mepolizumab vs. background therapy	■	■ Normal	3.3.3.2
Treatment effect for severe exacerbations: mepolizumab vs. background therapy	■	■ Normal	3.3.3.2
Treatment effect for moderate/severe exacerbations: mepolizumab vs. dupilumab	■	■ Normal	3.3.3.2
Treatment effect for severe exacerbations: mepolizumab vs. dupilumab	■	■ Normal	3.3.3.2
Treatment effect for moderate exacerbations in responders: mepolizumab vs. background therapy	■	■ Normal	3.3.3.3
Treatment effect for severe exacerbations in responders: mepolizumab vs. background therapy	■	■ Normal	3.3.3.3
Probability of discontinuation (year 1) - mepolizumab	Table 57	Beta	3.3.4

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Annual probability of discontinuation (year 1) - dupilumab	9.3%	Beta	3.3.4
Probability of discontinuation (year 2+)	Table 58	Beta	3.3.4
Background mortality	National life tables removing COPD	-	3.3.5.1
SMR	2.5	2.25, 2.75 Normal	3.3.5.2
CFR	15.6%	10.90%, 20.30% Beta	3.3.5.3
Quality of life			
Baseline utility (no exacerbations)	██████	██████████ Beta	3.4.1
Moderate (0–3 months) disutility	██████	██████████ Normal	3.4.1
Post-moderate disutility	██████	██████████ Normal	3.4.1
Severe (0–3 months) disutility	██████	██████████ Normal	3.4.1
Severe (3–6 months) disutility	██████	██████████ Normal	3.4.1
Severe (6–9 months) disutility	██████	██████████ Normal	3.4.1
Severe (9–12 months) disutility	██████	██████████ Normal	3.4.1
Post-severe (>12 months) disutility	██████	██████████ Normal	3.4.1
Frequent severe (0–3 months) disutility	██████	██████████ Normal	3.4.1
Frequent severe (3–6 months) disutility	██████	██████████ Normal	3.4.1
Frequent severe (6–9 months) disutility	██████	██████████ Normal	3.4.1
Frequent severe (9–12 months) disutility	██████	██████████ Normal	3.4.1
Cost inputs			
Treatment acquisition costs	Table 64	-	3.5.1.1
Treatment administration costs	£52 nurse visit, 95% self-admin for mepolizumab and dupilumab	-	3.5.1.2
COPD management costs	Table 65	Halved, doubled in OWSA	3.5.2.1
Moderate exacerbation resource use	Table 66	Halved, doubled in OWSA	3.5.2.2.1

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Severe exacerbation resource use	Table 67	Halved, doubled in OWSA	3.5.2.2.2

Abbreviations: CFR, case fatality rate; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume; OWSA, one-way sensitivity analysis; SMR, standardised mortality ratio

3.9.2 Assumptions

A summary of the model assumptions is provided in Table 71.

Table 71: Assumptions

Category	Assumption	Justification
Model structure and settings (Section 3.2.2)	Exacerbations are the most important determinant of health outcomes in this target population of COPD patients	In line with clinical opinion received by the Company and noted as part of the dupilumab NICE submission
	Patients who do not respond to treatment after 52 weeks or discontinue treatment with mepolizumab/ dupilumab receive SoC and have the exacerbation risks and impact as SoC patients	In line with expected clinical practice and the dupilumab NICE submission
	A severe exacerbation is a more significant factor in predicting patient outcomes (within the model) than a moderate exacerbation	Severe exacerbators are associated with increased risk of mortality and subsequent exacerbations, higher utility decrement, and increased HCRU compared with moderate exacerbators (247, 248)
	Patients cannot experience an exacerbation and discontinue in the same model cycle	In line with expected clinical practice and for ease of modelling outcomes
Clinical inputs (Section 3.3)	The treatment effect for responders is assumed to be the same in each moderate exacerbation state (0-3 months and ≥3 months) and severe exacerbation state (all severe/ frequent-severe timing states).	Observations were not sufficient to estimate RRs in each health state for responders to treatment
	No treatment effect waning on exacerbation reduction is included for responders to treatment with mepolizumab/ dupilumab	In line with the dupilumab NICE submission for exacerbation rates and 2-year MATINEE data
	Discontinuation rates in year 2+ were assumed to be the same for mepolizumab and dupilumab (█████% per model cycle)	Given the paucity of data after 52-weeks for dupilumab
HRQoL inputs (Section 3.4)	Costs and disutilities for adverse events are not included in the model	Adverse events are assumed not to be significantly different between treatments and are therefore excluded

Category	Assumption	Justification
Cost inputs (Section 3.5)	Mepolizumab and dupilumab are assumed to be self-administered in 95% of patients	In line with the EAG report in the dupilumab NICE submission (20)

Abbreviations: COPD, chronic obstructive pulmonary disease; EAG, evidence assessment group; HCRU, healthcare resource use; HRQoL, health-related quality of life; NICE, national institute of health and care excellence; RR, rate ratio; SoC, standard of care.

3.10 Base-case results

3.10.1 Base-case incremental cost-effectiveness analysis results

The base-case results are presented using the list price for SoC and dupilumab, and the PAS price (£[REDACTED] per 100mg pack) for mepolizumab. As described in section 3.2.3.2, the comparison with SoC is considered the primary (and most robust) comparison for decision making in this analysis, with the comparison with dupilumab included as an exploratory analysis.

Table 72 presents the fully incremental base-case deterministic results for mepolizumab compared with SoC, and dupilumab, as well as incremental net health benefit (NHB) of mepolizumab compared with SoC, and dupilumab, at willingness-to-pay (WTP) threshold values of £20,000 and £30,000 per QALY.

In the pairwise analysis, mepolizumab dominates dupilumab, and is associated with an ICER of £18,347 vs. SoC. The corresponding pairwise incremental NHB of mepolizumab compared with SoC and dupilumab is 0.35 and 2.39 respectively at the £30,000 per QALY WTP threshold.

Table 72: Base-case results (deterministic) – fully incremental analysis (mepolizumab PAS price)

	Total costs (£)	Total LYG	Total QALYs	Incr. costs	Incr. LYs	Incr. QALYs	ICER vs. SoC	ICER vs. Mepolizumab	Fully incremental ICER	NHB 20k (mepolizumab vs. comp)	NHB 30k (mepolizumab vs. comp)
SoC	■	■	■	-	-	-	-	-	-	0.07	0.35
Mepolizumab + SoC	■	■	■	■	■	■	£18,347	-	£18,347	-	-
Dupilumab + SoC	■	■	■	■	■	■	£120,738	Dominated	Dominated	3.47	2.39

Abbreviations: comp, comparator; ICER, incremental cost-effectiveness ratio; Incr, incremental; LYG, life years gained; NHB, net health benefit; PAS, patient access scheme; QALYs, quality-adjusted life years; SoC, standard of care.

Clinical outcomes from the model, and disaggregated results of the base-case incremental cost-effectiveness analysis are provided in Appendix H.

3.11 Exploring uncertainty

Probabilistic sensitivity analysis (PSA), deterministic one-way sensitivity analysis (OWSA) and deterministic and probabilistic scenario analysis was conducted in order to assess the impact of parameter uncertainty on the base-case model results.

3.11.1 Probabilistic sensitivity analysis

The PSA involved varying the inputs by randomly assigning a parameter value from predefined uncertainty distributions for each parameter in the model. Costs and outcomes were then recorded for 5,000 evaluations of the model with random sampling of parameters in each evaluation. Table 73 presents the outputs of the PSA comparison for mepolizumab vs. dupilumab and SoC; the corresponding scatterplot and cost-effectiveness acceptability curve (CEAC) are presented in Figure 12 and Figure 13, respectively.

The results are highly congruent with the deterministic results, and show positive incremental net health benefits at both a WTP threshold of £20,000 and £30,000.

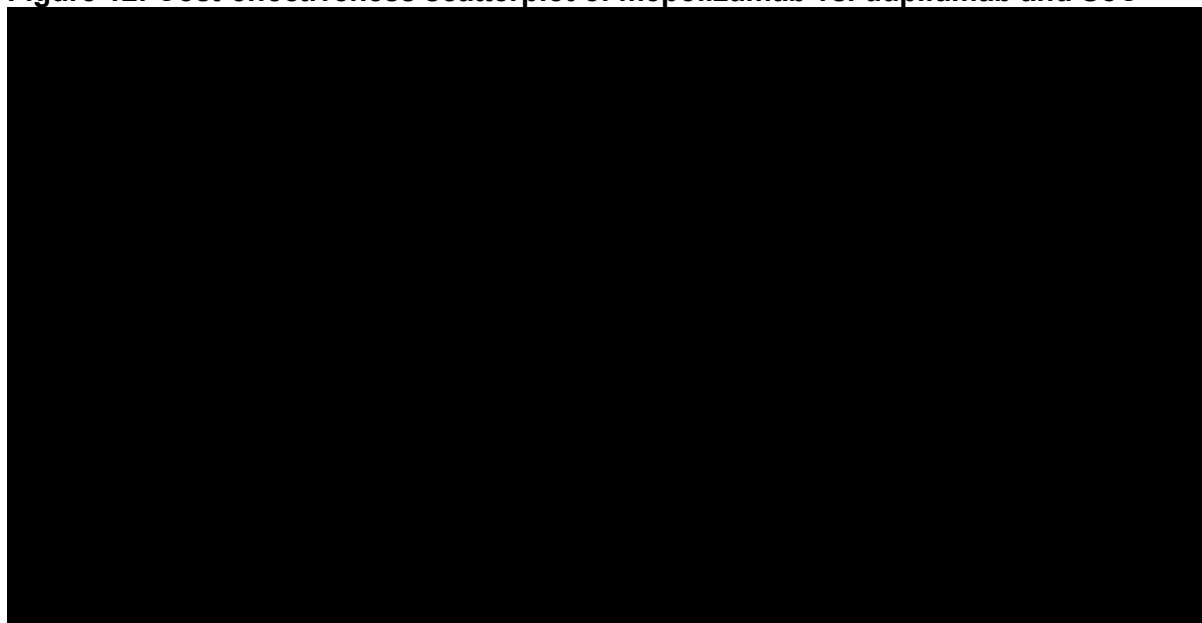
The CEAC shows that there is a 70.4% probability that mepolizumab is the most cost-effective option at a WTP threshold of £20,000, a probability of 96.5% at £25,000 and 99.7% probability at £30,000.

Table 73: Base-case results (probabilistic) (mepolizumab PAS price)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER vs. SoC	ICER vs. mepolizumab	Fully incremental ICER	Incr. NHB at £20,000 per QALY (mepolizumab vs. comp)	Incr. NHB at £30,000 per QALY (mepolizumab vs. comp)
SoC	■	■	=	=	-	-	-	0.07	0.35
Mepolizumab + SoC	■	■	■	■	£18,383	-	£18,383	-	-
Dupilumab + SoC	■	■	■	■	£134,920	Dominated	Dominated	3.49	2.43

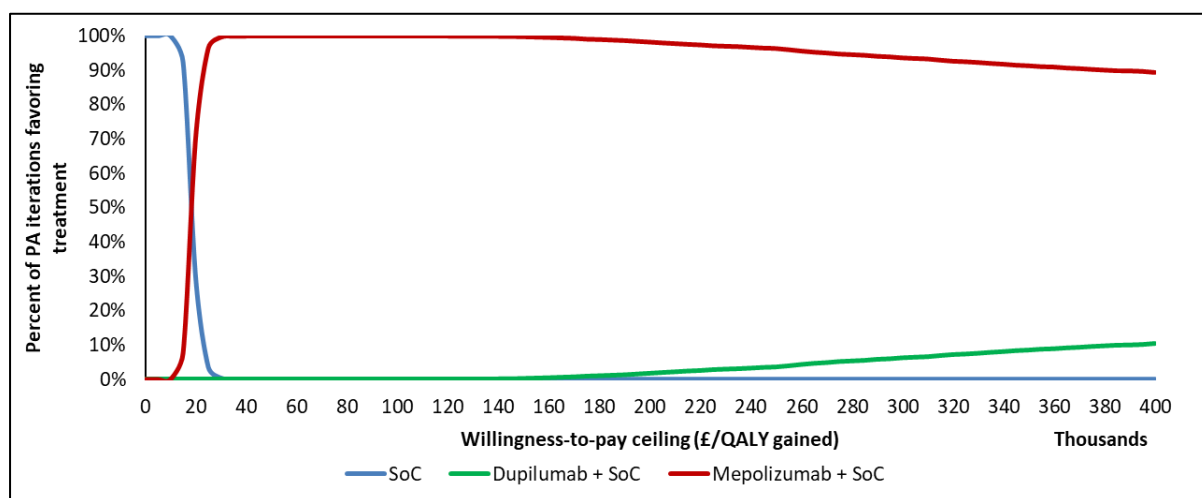
Abbreviations: comp, comparator; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life year; SoC, standard of care.

Figure 12: Cost-effectiveness scatterplot of mepolizumab vs. dupilumab and SoC



Abbreviations: Dupi, dupilumab; Mepo, mepolizumab; QALY, quality-adjusted life year; SoC, standard of care.

Figure 13: Cost-effectiveness acceptability curve of mepolizumab vs. dupilumab and SoC



Abbreviations: PA, probabilistic analysis; QALY, quality adjusted life year; SoC, standard of care.

3.11.2 Deterministic sensitivity analysis

A deterministic OWSA was conducted to explore the effect of uncertainty associated with varying individual model inputs. The OWSA involved varying one parameter at a time to upper

and lower confidence intervals^a (CI; the low value is the lower bound of the 95% CI, the high value is the upper bound of the 95% CI). In the absence of data, the CI was estimated by assuming $\pm 10\%$ around the mean value.

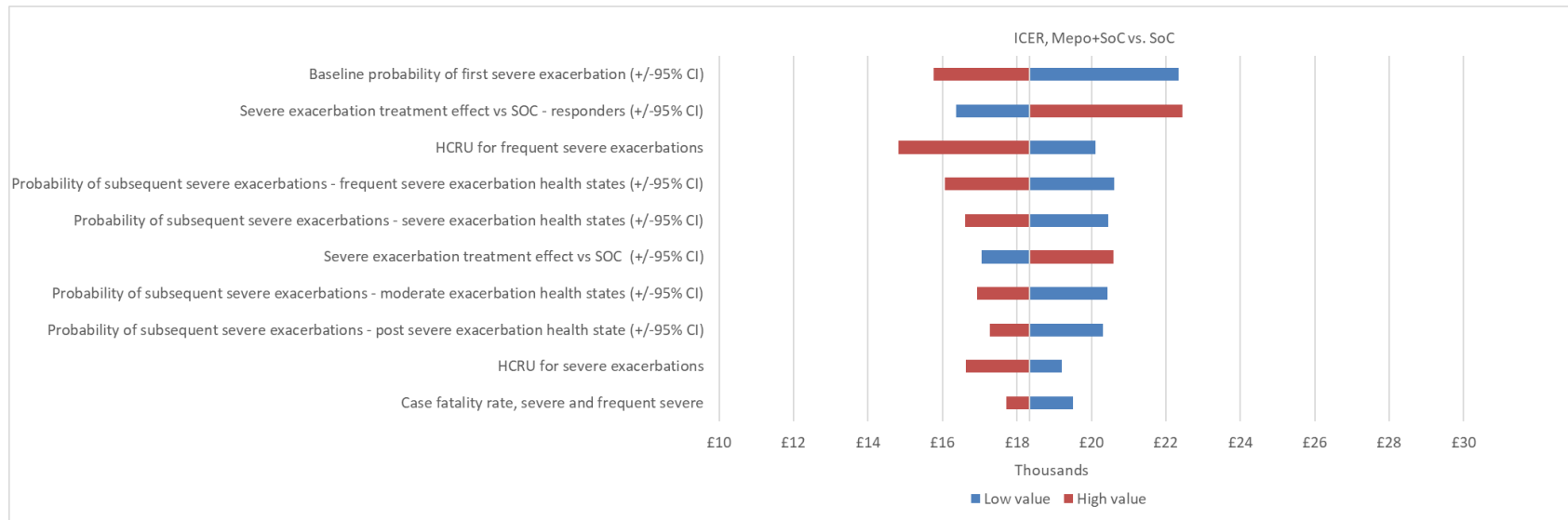
Figure 14 and Figure 15 present the results of the OWSA comparing mepolizumab with SoC and dupilumab, respectively. As dupilumab (at list price) is dominated by mepolizumab in the base-case analysis, the incremental NHB has been recorded at the upper and lower values of parameters for this comparison.

For the comparison of mepolizumab with SoC, the ICER was most sensitive to the baseline probability of first severe exacerbation, the severe exacerbation treatment effect for responders of mepolizumab, and the HCRU cost estimates in the severe and frequent-severe health states. The ICER remains below a £23,000 per QALY WTP threshold in all of the estimated OWSA results.

For the comparison of mepolizumab with dupilumab (at list price), the NHB was most sensitive to the severe exacerbation treatment effect for mepolizumab vs. dupilumab, and the SMR. The incremental NHB remained positive in all estimated OWSA results.

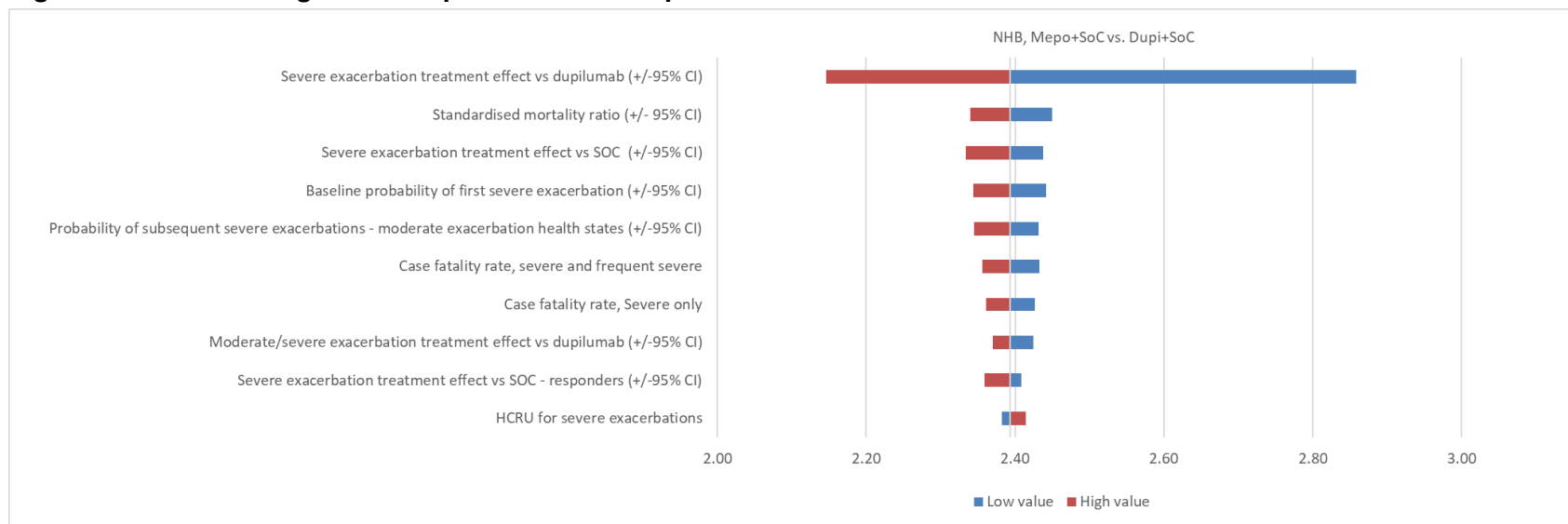
^a The risk of subsequent moderate and severe exacerbations following an initial exacerbation were not varied completely independently in the model i.e. split only by severity and not time since exacerbation. For example, the risk of a subsequent severe exacerbation is varied at the upper and lower bound jointly in the moderate (0-3 months) and moderate (>3 months) health states. This is likely to result in an overestimation of the impact of the uncertainty in these parameters on model results, however subsequent exacerbation rates impact all treatments and are not a large driver of cost-effectiveness.

Figure 14: Tornado diagram of mepolizumab vs. SOC



Abbreviations: CI, confidence interval; HCRU, healthcare resource use; ICER, incremental cost-effectiveness ratio; Mepo, mepolizumab; SOC, standard of care.

Figure 15: Tornado diagram of mepolizumab vs. dupilumab



Abbreviations: CI, confidence interval; dupi, dupilumab; HCRU, healthcare resource use; mepo, mepolizumab; NHB, net health benefit; SOC, standard of care.

3.11.3 Scenario analysis

A range of deterministic scenario analyses were conducted to test the robustness of the model to alternative model inputs and assumptions. A summary of the scenario analyses performed, with justification is presented in Table 74.

Table 74: Key scenario analyses

Base case assumption	Scenario detail	Rationale
3.5% annual discount rate for costs and outcomes	0% discount rate for costs and outcomes.	A 3.5% annual discount rate was selected in line with the NICE reference case. A 1.5% discount rate is included as a scenario analysis in line with suggestions in the NICE reference case, in addition to no discounting.
	1.5% discount rate for costs and outcomes.	
Lifetime (30-year) horizon	5-year time horizon.	A lifetime horizon was chosen in line with the NICE reference case which states that the time horizon should be long enough to reflect all important differences in costs and outcomes between the technologies being compared. Shorter time horizons are explored in scenario analyses to assess the impact.
	10-year time horizon.	
Baseline exacerbation rates sourced from the pooled trial analysis (MATINEE, METREX, METREO) including IMPACT, and ECLIPSE	Baseline exacerbation rates calibrated to prior year frequency from MATINEE trial.	The pooled trial analysis was selected to maximise the sample size in calculating baseline exacerbation rates. In order to evaluate the impact of potentially low exacerbation risks in clinical trials compared with real-world practice, higher baseline rates were tested in scenario analysis.
	Baseline exacerbation rates based on the METREX/ METREO trials.	
Exacerbation rate treatment effect in Year 1 sourced from the pooled mITT-300 analysis	Exacerbation rate treatment effect in year 1 sourced from the MATINEE trial only.	The pooled mITT-300 analysis was selected to maximise the sample size in calculating exacerbation rate ratios for mepolizumab. The confidence interval of the rate ratio for severe exacerbations vs. SoC in the base case crosses one. However, mepolizumab is associated with a statistically significant decrease in the rate of first severe exacerbations vs. SoC. Therefore, uncertainty is explored in the rates of severe exacerbations used for mepolizumab in the model, with one scenario considering the uncertainty surrounding subsequent exacerbations in particular.
	Exacerbation rate treatment effect in year 1 sourced from the pooled mITT-300, split by first and subsequent exacerbation. Subsequent exacerbation rate is set equal to first exacerbation rate.	
MAIC analysis considering patients with chronic bronchitis, determined by investigator	MAIC analysis considering patients with chronic bronchitis, determined using responses to the SGRQ-C questionnaire at baseline.	Investigator assessment was chosen as this better aligned with the approach used in the BOREAS/NOTUS trials to define chronic bronchitis. The SGRQ is used in scenario analysis to explore uncertainty around the approach.

Base case assumption	Scenario detail	Rationale
assessment at baseline		
Exacerbation rate treatment effect in Year 2+ (for responders) sourced from the pooled mITT-300 analysis	Exacerbation rate treatment effect in year 2+ (for responders) sourced from the MATINEE trial.	The pooled mITT-300 analysis was selected to maximise the sample size in calculating exacerbation rate ratios for mepolizumab. MATINEE is used in scenario analysis as data was available beyond 52 weeks.
Treatment discontinuation sourced from the MATINEE trial in year 2+ for mepolizumab and dupilumab	Treatment discontinuation sourced from the real-world evidence in year 2+ (15%).	MATINEE includes patient follow-up for up to 104 weeks and aligns with data used for mepolizumab for discontinuation in year 1. Alternative scenarios are tested in line with the rates used in the dupilumab NICE submission. A 15% annual rate is considered conservative given the range of values tested in the dupilumab NICE submission was 15% - 25.8%, and trial data is not available for dupilumab.
	Treatment discontinuation sourced from the real-world evidence in year 2+ (15%) for dupilumab and from MATINEE for mepolizumab.	
An SMR of 2.5 is applied to background mortality estimates for all health states	No SMR applied to background mortality estimates for all health states	An SMR was considered appropriate in the dupilumab NICE submission and reflects the increased risk of mortality in patients with severe COPD. Scenario analysis is performed to assess the impact, and in line with explorations tested by the EAG in the dupilumab NICE submission (20).
A CFR of 15.6% is applied to severe exacerbation health states	CFR of 14.2% applied to severe exacerbation health states	15.6% used in the base case and tested in scenario analysis in line with the value reported in the NRAP clinical outcomes (2021-23) and outliers summary report (39)
Baseline utility value taken from the pooled trial analysis including the IMPACT trial	Baseline utility value taken from the MATINEE trial only.	The pooled trial analysis was selected to maximise the sample size in estimating baseline utility. EQ-5D was not collected in the ECLIPSE trial and this was therefore not included in the pooling. Scenario analysis is performed to assess the consistency between trials.
Disutility values associated with each exacerbation state taken from the pooled trial analysis including the IMPACT trial	Disutility values associated with each exacerbation state taken from Jackson <i>et al.</i> , 2024.	The pooled trial analysis was selected to maximise the sample size in estimating disutility and align with the source of baseline utility values in the model. EQ-5D was not collected in the ECLIPSE trial and this was therefore not included in the pooling. In severe exacerbation health states, rates are associated with a wide confidence interval due to fewer observations. Therefore, they are explored in scenario analysis using values considered for scenario analysis in the dupilumab NICE submission. SGRQ was collected in the considered trials and has been mapped to EQ-5D using Starkie <i>et al.</i> , 2011 (281). An additional scenario analysis capping disutility in the post-severe state has
	Disutility values associated with each exacerbation state taken from Hoogendoorn <i>et al.</i> , 2011.	
	Disutility values associated with each exacerbation state sourced from trial SGRQ responses.	
	Disutility values associated with each exacerbation state taken from the pooled trial	

Base case assumption	Scenario detail	Rationale
	analysis including the IMPACT trial. Post-severe disutility set equal to severe (9-12 months) to prevent implausible outcomes.	been included as post-severe disutility appeared implausible compared with other severe health states.
Utility values are age-adjusted using Hernandez-Alava, 2022	No age adjustment is included.	In line with NICE guidance. Scenario analysis included to explore the impact.
Societal costs not included	Productivity loss and early retirement costs included in the model	Important to explore the potential impact on wider society

Abbreviations: CFR, case fatality rate; COPD, chronic obstructive pulmonary disease; EAG, evidence assessment group; mITT-300, modified intention-to-treat 300 (participants with BEC ≥ 300 cells/ μ L at screening who received ≥ 1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline; NICE, National Institute for Health and Care Excellence; SGRQ, St. George's Respiratory Questionnaire; SMR, standardised mortality ratio.

Scenario analysis results for the comparison of mepolizumab with SoC and dupilumab are presented in Table 75 and Table 76, respectively.

When compared to SoC, scenarios with the largest impact were those related to the time horizon, SMR, the perspective, and baseline exacerbation rates.

When compared to dupilumab (at list price), scenarios with the largest impact were those related to the time horizon, discount rates, long term discontinuation, SMR, and baseline exacerbation rates.

Table 75: Scenario analysis results vs. SoC

Scenario	Incremental costs	Incremental QALYs	Pairwise ICER (mepolizumab vs. SoC)	Difference
Base case	██████	██████	£18,347	-
Discount rate 0%	██████	██████	£16,051	-12.5%
Discount rate 1.5%	██████	██████	£16,991	-7.4%
Time horizon 5 years	██████	██████	£59,897	226.5%
Time horizon 10 years	██████	██████	£26,281	43.2%
Baseline exacerbation rate: Calibrated rate targeting MATINEE screening values	██████	██████	£11,640	-36.6%
Baseline exacerbation rate: from METREX/METREO	██████	██████	£15,403	-16.0%
Treatment effect (moderate and severe): MATINEE only	██████	██████	£17,814	-2.9%
Treatment effect (moderate and severe): Pooled mITT-300 trials (first exacerbation.; subsequent set equal)	██████	██████	£17,599	-4.1%

Scenario	Incremental costs	Incremental QALYs	Pairwise ICER (mepolizumab vs. SoC)	Difference
Treatment effect (responders): MATINEE only	██████	██████	£19,756	7.7%
Long-term discontinuation source: Trial data + 15% annual discontinuation	██████	██████	£18,494	0.8%
SMR of 1	██████	██████	£15,633	-14.8%
Severe Exacerbation case fatality rate of 14.2%	██████	██████	£18,615	1.5%
Baseline utility: MATINEE trial analysis (EQ-5D-3L UK)	██████	██████	£18,273	-0.4%
Disutility source: Jackson <i>et al.</i> , 2024	██████	██████	£18,282	-0.4%
Disutility source: Hoogendoorn <i>et al.</i> , 2011	██████	██████	£18,352	0.0%
Disutility source: Pooled trial analysis (SGRQi -> EQ-5D change)	██████	██████	£18,004	-1.9%
Disutility cap (Post-severe disutility set equal to severe (9-12 months))	██████	██████	£18,242	-0.6%
Utility adjustment for age	██████	██████	£18,347	0.0%
Societal perspective	██████	██████	£14,866	-19.0%

Abbreviations: EQ-5D, EuroQol five dimension; EQ-5D-3L, EuroQol five dimension three level; ICER, incremental cost-effectiveness ratio; LYG, life years gained; mITT-300, modified intention-to-treat 300 (participants with BEC ≥ 300 cells/ μ L at screening who received ≥ 1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline; QALYs, quality-adjusted life years; SGRQ, St Georges Respiratory Questionnaire; SMR, standardised mortality rate; SoC, standard of care.

Table 76: Scenario analysis results vs. dupilumab

Scenario	Incremental costs	Incremental QALYs	Incremental NHB (mepolizumab vs. dupilumab)	Difference
Base case	██████	██████	2.39	-
Discount rate 0%	██████	██████	2.92	22.0%
Discount rate 1.5%	██████	██████	2.67	11.5%
Time horizon 5 years	██████	██████	1.38	-42.3%
Time horizon 10 years	██████	██████	2.03	-15.4%
Baseline exacerbation rate: Calibrated rate targeting MATINEE screening values	██████	██████	2.12	-11.5%
Baseline exacerbation rate: from METREX/METREO	██████	██████	2.30	-3.8%
Treatment effect (moderate and severe): MATINEE only	██████	██████	2.41	0.7%
Treatment effect (moderate and severe): Pooled mITT-300 trials (first exacerbation.; subsequent set equal)	██████	██████	2.42	1.1%

Scenario	Incremental costs	Incremental QALYs	Incremental NHB (mepolizumab vs. dupilumab)	Difference
MAIC CB definition (SGRQ-C self-report)	██████	██████	2.25	-5.8%
Treatment effect (responders): MATINEE only	██████	██████	2.38	-0.5%
Long-term discontinuation source: Trial data + 15% annual discontinuation	██████	██████	1.77	-26.0%
Long-term discontinuation source: Trial data + separate rates for mepo and dupi	██████	██████	1.87	-21.8%
SMR of 1	██████	██████	2.81	17.5%
Severe Exacerbation case fatality rate of 14.2%	██████	██████	2.40	0.5%
Baseline utility: MATINEE trial analysis (EQ-5D-3L UK)	██████	██████	2.39	0.0%
Disutility source: Jackson <i>et al.</i> , 2024	██████	██████	2.38	-0.6%
Disutility source: Hoogendoorn <i>et al.</i> , 2011	██████	██████	2.38	-0.6%
Disutility source: Pooled trial analysis (SGRQi -> EQ5D change)	██████	██████	2.40	0.2%
Disutility cap (Post-severe disutility set equal to severe (9-12 months))	██████	██████	2.39	-0.3%
Utility adjustment for age	██████	██████	2.39	0.0%
Societal perspective	██████	██████	2.39	-0.1%

Abbreviations: EQ-5D, EuroQol five dimension; EQ-5D-3L, EuroQol five dimension three level; ICER, incremental cost-effectiveness ratio; LYG, life years gained; mITT-300, modified intention-to-treat 300 (participants with BEC ≥ 300 cells/ μ L at screening who received ≥ 1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline; QALYs, quality-adjusted life years; SGRQ, St Georges Respiratory Questionnaire; SMR, standardised mortality rate; SoC, standard of care.

3.11.3.1 Cost comparison mepolizumab vs. dupilumab

As outlined in the decision problem (Section 1.1) for this appraisal, GSK believes that a CC against dupilumab is appropriate, should dupilumab receive positive NICE guidance, given that the MAIC showed numerical trends favouring mepolizumab, with no statistically significant differences across exacerbation and HRQoL outcomes, indicating at least broadly similar health benefits between treatments. Clinical expert opinion has also indicated that mepolizumab would provide at least similar health benefits to dupilumab in this population of patients with COPD (245). This aligns with the NICE guidance for a CC case, which states that a case can be made if a health technology provides similar or greater health benefits at a similar or lower cost than comparator treatments (308). A CC analysis has therefore been

detailed below, with results regarding the cost savings associated with mepolizumab in comparison with dupilumab (at list price).

3.11.3.1.1 Features of the cost-comparison analysis

A CC model was built in Microsoft® Excel to evaluate the cost to the NHS associated with the introduction of mepolizumab compared with dupilumab in adult patients with uncontrolled COPD (defined as ≥ 2 moderate or ≥ 1 severe exacerbations within 12 months) of an eosinophilic phenotype (defined as having blood eosinophil count of ≥ 300 cells/ μ L) on a combination of an ICS, a LABA, and a LAMA.

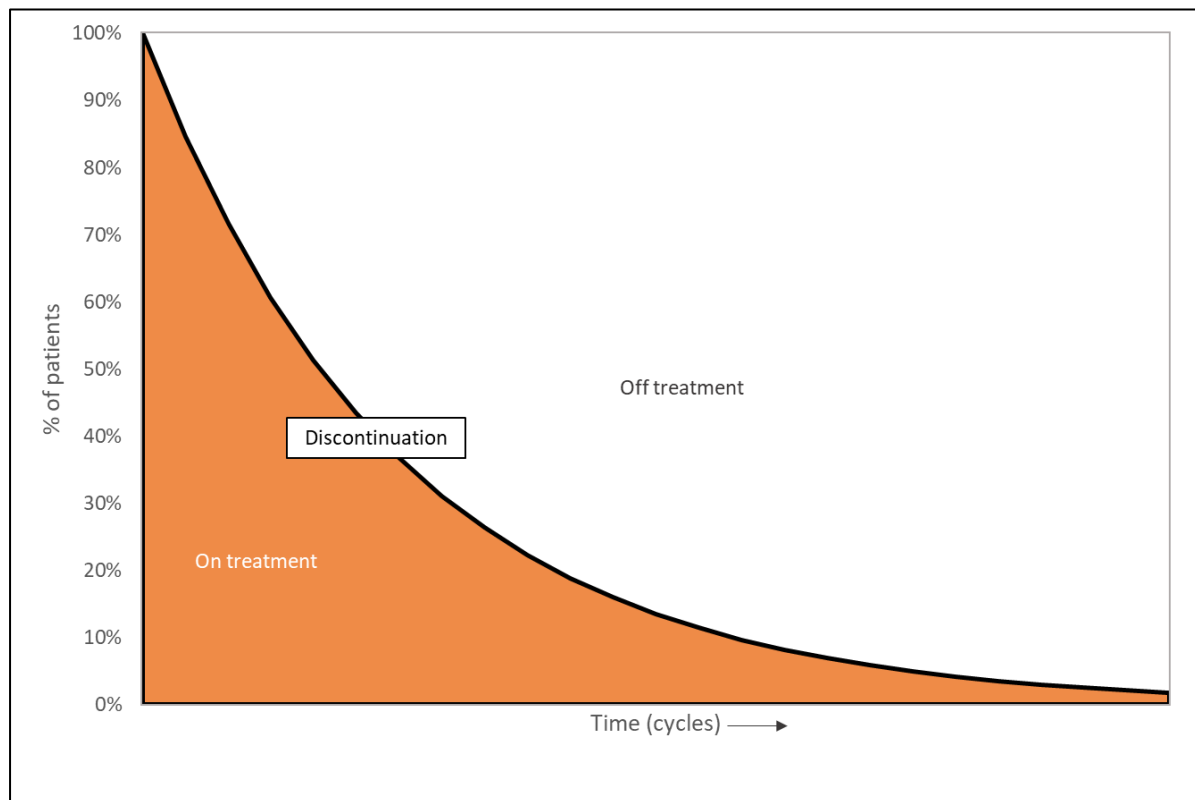
Dupilumab was selected as the most appropriate comparator for the cost-comparison analysis as outlined in Section 1.4.6.

A 10-year time horizon was adopted, to capture all relevant cost differences between modelled treatments. A 5-year time horizon was considered in a scenario analysis. In line with the CEM, a cycle length of 3 months was modelled, and half-cycle correction was applied. No discounting was assumed, as timings of cost streams between treatments is considered similar and hence discounting is not expected to impact incremental results. Scenarios were tested including discounting (at 3.5% and 1.5%)

3.11.3.1.2 Model structure

The analysis was structured as a 2-state model which included on- or off-treatment status with either mepolizumab or dupilumab (Figure 16). Treatment status was defined by discontinuation rates observed in the pooled mITT-300 trial data in year one, and then from MATINEE beyond the first year.

Figure 16: Cost-comparison model structure



The analysis considered costs associated with treatment acquisition and administration only as these costs are expected to be the key drivers of cost differences between arms.

The model assumed all patients begin on treatment with mepolizumab or dupilumab and receive a treatment regimen consistent with the SmPC for each treatment. Three-month discontinuation probabilities are calculated separately for the first year and subsequent years.

An overview of the cost-comparison analysis is presented in Table 77.

Table 77: Features of the cost-comparison analysis

Component	Approach
Population	Adult patients with uncontrolled COPD (defined as ≥ 2 moderate or ≥ 1 severe exacerbations within 12 months) of an eosinophilic phenotype (defined as having blood eosinophil count of ≥ 300 cells/ μ L) on a combination of an ICS, a LABA, and a LAMA.
Intervention	Mepolizumab 100 mg administered SC Q4W
Comparator	Dupilumab 200 mg administered SC Q2W
Outcomes	- Incremental costs per patient - Total costs per patient
Perspective	NHS and PSS in England and Wales
Time horizon	10 years 5-year time horizon considered in scenario analysis
Discounting	0% discount rate for costs 3.5% annual discount rate for costs considered in scenario analysis

Company evidence submission for mepolizumab for treating chronic obstructive pulmonary disease with an eosinophilic phenotype [ID1237]

Component	Approach
	1.5% annual discount rate for costs considered in scenario analysis

Abbreviations: COPD, chronic obstructive pulmonary disorder; ICS, inhaled corticosteroids; LABA, long-acting beta₂-agonist; LAMA, long-acting muscarinic antagonist; NHS, National Health Service; PSS, Personal Social Services; Q2W, once every 2 weeks; Q4W, once every 4 weeks; SC, subcutaneous.

3.11.3.1.3 Treatment continuation and discontinuation

Three-month discontinuation probabilities were modelled and a simplifying assumption was taken where discontinuation probabilities were assumed equal for both modelled treatments. Rates for the first year were derived from the pooled mITT-300 trial data and used to estimate 3-month probabilities of discontinuation and are presented in Table 78 (21). This is considered conservative given that discontinuation rates used in the dupilumab NICE submission within the first year are lower, which would result in higher treatment costs (estimated 2.41% discontinuation per 3-month cycle).

MATINEE was used to estimate a discontinuation probability from Year 2 onwards (█% per cycle) for both modelled treatments, with alternative rates of discontinuation considered in scenario analyses. Trial data for dupilumab was not collected after 52-weeks and therefore, a 15% annual discontinuation rate was used in the dupilumab NICE Company submission based on RWE from an asthma study and clinical expert opinion to the Company (20, 250-252). This is used for mepolizumab and dupilumab for Year 2 onwards in scenario analysis and translates to a per cycle probability of discontinuation of 3.68%. For completeness, a scenario analysis is performed where the █% per cycle probability of discontinuation from MATINEE is assumed for mepolizumab and the 3.68% per cycle probability of discontinuation is assumed for dupilumab for Year 2 onwards in the model.

Table 78: Treatment discontinuation probabilities

	N on treatment	N discontinuing	3-month discontinuation probability	Source
0–3 months	█	█	█	pooled mITT-300 analysis (27)
4–6 months	█	█	█	
7–9 months	█	█	█	
10–12 months	█	█	█	
Subsequent cycles	█	█	█	

Abbreviations: mITT-300, modified intention-to-treat 300 (participants with BEC ≥300 cells/μL at screening who received ≥1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline).

After the first year, only patients who are judged to have responded to treatment (in line with the continuation rule described in Section 3.3.2), continue treatment over the modelled time horizon (Table 79). The responder rate is assumed to be the same between treatments for

simplicity, given that between trial differences exist, but observed overall response rates between mepolizumab and dupilumab trials were similar.

Table 79: Treatment continuation probabilities

	Value	Source
Number on treatment	██████	MATINEE trial (21)
Number meeting responder criteria	██████	
Year 1 responder rate	██████	Calculated

3.11.3.1.4 Drug acquisition and administration costs

Drug acquisition

A summary of the acquisition costs associated with mepolizumab and dupilumab are presented in Table 80. Drug acquisition costs were sourced from GlobalData POLI, which uses prices of drugs from the UK's Dictionary of Medicines and Devices, aligned with the source used by the BNF (300). For mepolizumab, a confidential Patient Access Scheme (PAS) discount of █████% is in place, resulting in a net price of £████ per 100 mg per 1 mL solution. Dosing schedules were aligned with SmPC for each treatment.

Table 80: Drug acquisition costs

Treatment	Dose per administration (mg)	Number of units	Price per vial	Days per dose	Cost per 3-month cycle
Mepolizumab	100	1	List price: £840.00	28	£2,739.38
			PAS price: █████		██████
Dupilumab	300	2	£1,264.89	28	£4,125.01

Abbreviations: PAS, patient access scheme.

Drug administration

A summary of drug administration costs is presented in Table 81. It was assumed that a proportion of patients self-administer treatment with mepolizumab or dupilumab and the rest require a nurse home visit for each routine administration. For patients who self-administer, a one-off cost of 1 hour of nurse time associated with training for self-injection is assumed. This is aligned with the approach preferred by the EAG in the dupilumab NICE submission.

Table 81: Administration costs

Parameter		Value	Source
% self-administration	Mepolizumab	95%	Dupilumab NICE submission
	Dupilumab	95%	Dupilumab NICE submission (20)
Self-administration	Training (one-off)	£52.00	One hour of band 5 nurse time, PSSRU 2023/24 (301)

Parameter	Value	Source
Nurse administration (per administration)	£52.00	One hour of band 5 nurse time, PSSRU 2023/24 (301)

Abbreviations: NICE, National Institute for Health and Care Excellence; PSSRU, Personal Social Services Research Unit.

The total administration cost of mepolizumab and dupilumab in the first and subsequent cycles are presented in Table 82.

Table 82: Total administration costs

	Administration costs	
	First cycle	Subsequent cycles
Mepolizumab	£57.88	£8.48
Dupilumab	£66.36	£16.96

3.11.3.1.5 Uncertainties in the inputs and assumptions

A summary of the inputs and assumptions used in the cost-comparison model is presented in Table 83 and Table 84, respectively.

Table 83: Summary of model inputs

Input	Value	Justification	Explored in sensitivity/ scenario analysis	
Time horizon (years)	10 years	In line with NICE reference case (199)	Scenario analysis 5 years	
Discount rate (%)	0%	Short time horizon	Scenario analysis 3.5% 1.5%	
Acquisition costs (per dose)				
Mepolizumab	List price: £840.00 PAS price: [REDACTED]	GlobalData POLI (300)	No – no uncertainty	
Dupilumab	List price: £1,264.89	GlobalData POLI (300)	No – no uncertainty	
Administration costs (per dose)				
Proportion self-administration	Mepolizumab	95%	Dupilumab NICE submission (20)	No – equal for mepolizumab and dupilumab
	Dupilumab	95%		
Self-administration training	£52.00	One hour of band 5 nurse time, PSSRU 2023/24 (301).	In line with dupilumab NICE submission (20)	No – equal for mepolizumab and dupilumab
Nurse administration	£52.00			No – equal for mepolizumab and dupilumab
Treatment discontinuation – 3-month probability				
0–3 months	[REDACTED]	Pooled mITT-300 analysis) (27)	Subsequent cycles, 15% annual discontinuation rate	
3–6 months	[REDACTED]			

Company evidence submission for mepolizumab for treating chronic obstructive pulmonary disease with an eosinophilic phenotype [ID1237]

Input	Value	Justification	Explored in sensitivity/ scenario analysis
6–9 months	██████		tested in scenario analysis in line with the dupilumab NICE submission (20)
9–12 months	██████		
Subsequent cycles	██████		
Treatment continuation at Year 1			
Responder rate	██████	MATINEE trial (21)	No – assumed equal for mepolizumab and dupilumab

Abbreviations: NICE, National Institute for Health and Care Excellence; mITT-300, modified intention-to-treat 300; PAS, patient access scheme; POLI, pharmaceutical price; PSSRU, Personal Social Services Research Unit; TA, technology appraisal.

Table 84: Summary of key model assumptions

Assumption	Rationale	Explored in sensitivity/scenario analysis
Treatment discontinuation in year 1 assumed to be the same for mepolizumab and dupilumab	The pooled mITT-300 trial data is used for both mepolizumab and dupilumab. This is considered conservative given that discontinuation rates used in the dupilumab NICE submission within the first year are lower (estimated 2.41% discontinuation per 3-month cycle) and hence more patients would remain on treatment and accumulate costs.	–
Discontinuation rates in year 2+ were assumed to be the same for mepolizumab and dupilumab (██████% per model cycle)	The MATINEE trial data is used for both mepolizumab and dupilumab to align with the approach used in year one and given the paucity of trial data after one year for dupilumab.	Scenario analysis included using 15% annual discontinuation rate from the dupilumab NICE submission for both treatments (20). Further scenario uses MATINEE for mepolizumab, and 15% annual discontinuation for dupilumab.
The responder probability (treatment continuation) at Year 1 is treatment-independent	Responder probability at 52 weeks between mepolizumab and dupilumab trials was similar, however there are between trial differences. For simplicity they are assumed to be the same between treatments in the CC analysis.	–
Mepolizumab and dupilumab are assumed to be self-administered in 95% of patients	In line with the EAG in the dupilumab NICE submission (20)	–

Abbreviations: CC, cost-comparison; EAG, Evidence assessment group; mITT-300, modified intention-to-treat 300; NICE, National Institute for Health and Care Excellence.

3.11.3.1.6 Base-case results

The base-case results are presented using the list price for dupilumab, and the net price with PAS (£██████ per 100mg pack) for mepolizumab.

Company evidence submission for mepolizumab for treating chronic obstructive pulmonary disease with an eosinophilic phenotype [ID1237]

Mepolizumab is associated with a cost-saving of [REDACTED] when compared with dupilumab (at list price) over a 10-year time horizon.

Table 85: Base-case results – mepolizumab PAS price

	Mepolizumab	Dupilumab	Incremental
Drug acquisition	[REDACTED]	£103,630	[REDACTED]
Drug administration	[REDACTED]	£475	[REDACTED]
Total costs	[REDACTED]	£104,104	[REDACTED]

Abbreviations: PAS, patient access scheme.

3.11.3.1.7 Sensitivity analysis

Results of sensitivity analysis, using the PAS price for mepolizumab, are presented in Table 86. A [REDACTED] had the largest impact on the base-case results [REDACTED]

Table 86: Sensitivity analysis results – mepolizumab PAS price

Scenario	Incremental cost	% difference
Base case	[REDACTED]	[REDACTED]
Time Horizon = 5 years	[REDACTED]	[REDACTED]
1.5% discount rate	[REDACTED]	[REDACTED]
3.5% discount rate	[REDACTED]	[REDACTED]
15% annual discontinuation rate for year 2 onwards (mepolizumab and dupilumab)	[REDACTED]	[REDACTED]
15% annual discontinuation rate for year 2 onwards (dupilumab only)	[REDACTED]	[REDACTED]

Abbreviations: PAS, patient access scheme.

3.11.3.1.8 Interpretation and conclusions of economic evidence

The CC analysis for mepolizumab and dupilumab considered drug acquisition and administration costs across a 10-year time horizon. Base-case and scenario analysis demonstrate cost-savings for mepolizumab, when assuming a net price of £[REDACTED] per 100 mg per 1 mL solution for adult patients with uncontrolled COPD of an eosinophilic phenotype (defined as having blood eosinophil count of ≥ 300 cells/ μ L) on a combination of an ICS, a LABA, and a LAMA.

3.12 Subgroup analysis

Subgroups were not considered in the cost-effectiveness or CC model.

3.13 Benefits not captured in the QALY calculation

As highlighted in Section 1.5, COPD disproportionately impacts patients from lower socio-economic backgrounds, who as a result are at higher risk of experiencing exacerbations and hospitalisations (49, 50). Mepolizumab would introduce a well-tolerated and effective option

Company evidence submission for mepolizumab for treating chronic obstructive pulmonary disease with an eosinophilic phenotype [ID1237]

for patients with COPD, with 95% of patients expected to self-administer, reducing administrative burden from the 4-weekly dosing schedule, reducing barriers to accessing treatment such as travel costs and time constraints and as a result, potentially decreasing socio-economic healthcare inequalities.

COPD exacerbations can increase the likelihood of hospitalisation, the risk of mortality, CV events, and contributes to disease progression whilst also increasing the risk of future exacerbations. Exacerbations and hospitalisations represent the major cost drivers in COPD management, accounting for the greatest proportion of the total economic burden of the disease (10). The estimated costs of managing moderate and severe exacerbations in England is predicted to rise from £0.6 billion in 2011 to over £1 billion by 2030 (40). The introduction of effective self-administered treatments such as mepolizumab would help reduce economic burden and relieve pressures on the NHS, including seasonal pressures which are amplified through respiratory diseases such as COPD in particular, given the high prevalence of COPD in the UK (1).

There is also a significant caregiver burden associated with COPD exacerbations in the UK (Section 1.4.3.2.5). In a UK COPD patient voices report, caregivers highlighted the personal costs of their caring role, which has a significant impact on their own relationships, work, finances, and personal time (43). This could translate into caregiver disutility and healthcare costs which have not been accounted for in the model. The introduction of mepolizumab, which has been shown to significantly reduce the annualised rate of moderate/severe exacerbations vs. background therapy, could decrease the burden of informal care provided by caregivers substantially.

Additionally, the cost-effectiveness analysis vs. SoC is estimated using a wider population definition than that used for the indirect comparison with dupilumab, due to the dupilumab and mepolizumab trials differing on some inclusion/exclusion criteria (Section 2.10.2). As shown in Table 35, trends in the MAIC suggest that the relative effect of mepolizumab vs. SoC may increase in the narrower “restricted population” used for the comparison with dupilumab, potentially increasing the cost-effectiveness of mepolizumab vs. SoC. This was not explored explicitly in the cost-effectiveness model.

3.14 Validation

3.14.1 Validation of cost-effectiveness analysis

Technical validation of the CEM was conducted to ensure that potential errors and omissions or bias from an individual analyst were addressed, including the following steps:

Company evidence submission for mepolizumab for treating chronic obstructive pulmonary disease with an eosinophilic phenotype [ID1237]

- An audit of input variables (to ensure accuracy of data entry from the original source material).
- Verification of formulae and programming code through tracing and/or generation of some key outcomes employing the same dataset.
- Analysis of the model results to ensure that they accurately reflect model inputs. Extreme values were used to test whether the model results reflect the expected impact of parameter changes.

The validation process was conducted by a senior analyst not involved in the original model programming. Corrections suggested by the reviewer were adopted prior to finalising the results and report.

3.14.2 External Validation

The model structure and assumptions have been validated by clinicians. The CEM was also externally validated by comparing outcomes to published models and real-world estimates. As highlighted in Section 3.1, no existing cost-effectiveness studies of mepolizumab in COPD have been published, however the face validity of outcomes for the SoC comparator has been assessed.

The modelled SoC arm outcomes aligned well with outcomes reported in the published literature.

Table 87: External validation of SoC model outcomes

Source	Outcome	Reference
Median Survival		
Mepolizumab CEM base case (SoC arm)	██████	Mean undiscounted LYs in the model
Dupilumab CEM base case	8.3 years	Median survival – dupilumab NICE ACM2 slides [†]
England - HES database (2010-2019)	6.9 years	Median survival – dupilumab NICE ACM2 slides [†]
France – BREATHE study (2015-2021)	8.7 years	Median survival – dupilumab NICE ACM2 slides [†]
USA – MarketScan database (2018-2022)	8.5 years	Median survival – dupilumab NICE ACM2 slides [†]
Total number of exacerbations		
Mepolizumab CEM base case (SoC arm)	██████	Mean total number of exacerbations in the model
Samyshkin 2014	15.64	Samyshkin <i>et al.</i> , 2014 (255)

[†]Note that the committee slides from ACM2 (August 2025) are not yet publicly available. The estimates presented here are based on information obtained through attendance at the ACM2 online meeting
Abbreviations: ACD, appraisal consultation document; ACM, appraisal committee meeting; CEM, Cost-effectiveness model; EAG, evidence assessment group; HES, Hospital episode statistics; LY, life years; PAS,

3.15 Interpretation and conclusions of economic evidence

At the PAS price, mepolizumab is associated with an ICER of £18,347 per QALY gained vs. SoC, which is below the £20,000 per QALY WTP threshold. When compared to the list price of dupilumab, the ICER is dominant for mepolizumab.

Deterministic and probabilistic sensitivity analyses were undertaken to assess the impact of testing uncertainty in the model inputs and assumptions. The mean probabilistic ICER vs. SoC (£18,383 per QALY) aligns closely with the deterministic ICER, indicating that the model results are robust to variance of inputs around their probabilistic distribution. At a £20,000 per QALY, £25,000 per QALY and £30,000 per QALY WTP threshold, mepolizumab was cost-effective in 70.4%, 96.5% and 99.7% of simulations, respectively.

For the comparison of mepolizumab with dupilumab (at list price), NHB remained positive in all situations in which parameters were varied in the OWSA at their upper and lower bounds, with the key model driver being the severe exacerbation treatment effect for mepolizumab vs. dupilumab. For the comparison of mepolizumab with SoC, for all OWSA scenarios the ICER value remained below £23,000 per QALY gained, with the baseline exacerbation rates and treatment effect of mepolizumab resulting in the most substantial impact.

Across the 19 scenario analyses tested, the ICER remained under the NICE £20,000 per QALY WTP threshold in 17 scenarios for the comparison with SOC, showing the robustness of the model results, with the two other scenarios related to shortening the model time horizon. Dupilumab remained dominated by mepolizumab in all but one of the considered scenarios, and mepolizumab was cost-effective in the remaining scenario.

As outlined in the decision problem (Section 1.1) for this appraisal, GSK believes that, should dupilumab receive timely positive NICE guidance, a cost-comparison of mepolizumab vs. dupilumab would be appropriate, given that the MAIC showed comparable numerical trends and no statistically significant differences in exacerbation and HRQoL outcomes between treatments, indicating at least similar or greater health benefit. In the cost-comparison analysis of mepolizumab and dupilumab, mepolizumab is associated with a cost-saving of £[REDACTED] when compared with the list price of dupilumab over a 10-year time horizon. Mepolizumab remains cost saving over all the considered sensitivity analyses.

3.15.1 Strengths of the cost-effectiveness analysis

Where appropriate, the model has been aligned with the NICE reference case perspective, as well as the inputs and assumptions used in the dupilumab NICE submission, where these were considered appropriate by the Committee and EAG (20).

Use of an exacerbation-based model structure aligns with the GOLD pharmacological treatment algorithm where treatment recommendations are based on exacerbation history and enables the assessment of treatment effect of mepolizumab on exacerbations. Consultation with clinical experts has also confirmed exacerbations to be the most important determinant of health outcomes in this population (245).

Inputs in the model are informed by multiple large and robust clinical studies, including three studies (MATINEE, METREX, and METREO) which show a significant and meaningful treatment effect in reducing exacerbations for mepolizumab vs. SoC. Data from the IMPACT and ECLIPSE trials has also been used to help inform baseline exacerbation inputs in the model, to ensure that the most robust comparison vs. SoC could be conducted. The inclusion of tunnel states in the model also allows the short-term and long-term impact of exacerbations to be captured. Importantly, the MATINEE trial included patient follow-up beyond 52 weeks, showing a consistent and maintained treatment effect for mepolizumab in reducing exacerbations.

The predicted mortality output in the CEM for the SoC arm is consistent with other published sources, and the ICER for mepolizumab is robust to the extensive exploration of uncertainty in the model, with a deterministic ICER that is very similar to the probabilistic ICER.

3.15.2 Limitations of the cost-effectiveness analysis

Data was pooled from five COPD trials to estimate SoC exacerbation rates in the model, to use as much data as possible. Of note, 34% of the patients in the pooled trial analyses were on dual therapy. However, it was considered that the most important predictor of future exacerbations is exacerbation history, therefore this data was still deemed informative to inform exacerbation rates in the model. Additionally, it should be noted that one of the studies in the pooled analyses is ECLIPSE, which was an observational study and could contribute to some heterogeneity due to differences in patient follow-up visits. However, less than 5% of the patients in the pooled population came from the ECLIPSE study; hence impact of including the ECLIPSE trial to heterogeneity should be minimal.

Due to lack of sufficient data on subsequent exacerbation events in the mepolizumab clinical trials, treatment effects on moderate and severe exacerbations were extrapolated based on

Company evidence submission for mepolizumab for treating chronic obstructive pulmonary disease with an eosinophilic phenotype [ID1237]

the overall reduction during the follow-up period from the pooled mITT-300 (MATINEE, METREX, METREO) trials (a similar approach was followed for treatment effect in the responders), and the same treatment effect was applied to first exacerbation in the model as well as subsequent exacerbations (as an overall reduction in exacerbations). A scenario was tested whereby reductions in first and subsequent exacerbations were considered separately, assuming the treatment effect on reducing subsequent exacerbations is the same as that of the first exacerbation. This had minimal impact on the results.

Mortality estimates for mepolizumab and SoC are informed by national life tables and the literature. A CFR associated with a severe exacerbation was used in the model, and it was assumed that the CFR for those experiencing frequent severe exacerbations is equal to that for first severe exacerbations. As frequent severe exacerbations experienced within 12 months of an initial severe exacerbation may well have increased risks for mortality (11, 16), this assumption may underestimate case-fatality rates for those experiencing frequent severe exacerbations.

Cost of frequent severe exacerbations were also assumed to be the same as cost of severe exacerbations. This could also be considered a conservative approach, as it is likely that patients who experience another severe exacerbation within 12 months of an initial severe exacerbation may have an increase in HCRU, and hence higher associated costs (11, 16).

Additionally, one- and two- year treatment discontinuation rates in the model were based on data from the mepolizumab trials but no data was available for treatment discontinuation in subsequent years (after year 2). Hence, for the reference case, the second-year rate of discontinuation from the MATINEE trial was assumed for subsequent years. In scenario analyses, alternative discontinuation rates beyond the first year were tested, and also assuming different long-term discontinuation rates for mepolizumab and dupilumab.

A limitation of the cost-effectiveness analysis relates to the incorporation of dupilumab as an exploratory comparator in the analysis using an indirect comparison due to the lack of direct head-to-head clinical data. The study populations between mepolizumab and dupilumab trials differed on several inclusion/exclusion criteria and baseline characteristics, despite the consistent elements of the study inclusion criteria (prior exacerbation frequency and eosinophilic phenotype). Adding to the complexity of the analysis, treatment effect outcomes were also not reported for risk of moderate exacerbation alone for dupilumab, therefore the approach to integrating the available data relied on the estimate of the severe exacerbation risk and overall exacerbation risk (moderate or severe) for the dupilumab + SoC arm and the difference between these two risks was used to determine the risk of moderate exacerbation.

Some information in the ongoing dupilumab NICE submission is also redacted, adding to the difficulty of comparison. Therefore, given the inherent uncertainty in the MAIC, which is propagated directly into the output of the economic model, as well as the other limitations mentioned in implementing dupilumab into the model, the cost-effectiveness analysis against dupilumab is considered exploratory. A cost-comparison analysis against dupilumab (at list price) was also conducted (see Section 3.11.3), with mepolizumab shown to be cost saving.

The comparison of mepolizumab vs. SoC in the cost-effectiveness analysis is based on a treatment effect estimated from data in the pooled mITT-300 trials (MATINEE, METREX, METREO). However, as detailed in Section 2.10.2, the “restricted populations” were used in the ITC compared to dupilumab in order to align with the dupilumab trials, which differed to the mepolizumab trials on inclusion/exclusion criteria. As shown in Table 35, trends in the MAIC suggest that using the adjusted “restricted population” may result in an increase in the relative effect of mepolizumab vs. placebo and therefore, the cost-effectiveness of mepolizumab vs. SoC could be greater if the analysis was based on a population aligned with that of the dupilumab trials. Cost-effectiveness has not been estimated for mepolizumab vs. SoC in this population.

3.15.3 Conclusion

A substantial proportion of patients with COPD continue to experience frequent exacerbations and poor outcomes. Currently, treatment options are limited for COPD patients with an eosinophilic phenotype who continue to exacerbate despite triple inhaled therapy, and there are no targeted biologic therapies routinely available within the NHS currently. Exacerbations are a leading cause of morbidity and mortality for patients with COPD due to the short-term impacts on lung function and QoL and long-term impacts on disease progression (10, 12, 38, 81)). Exacerbations are also costly events for the NHS, with COPD exacerbations being the leading contributor to the overall economic burden of COPD. The estimated cost of managing moderate and severe exacerbations in England is predicted to rise from £0.6 billion in 2011 to over £1 billion by 2030 (40). Given this unmet need, and the poor outcomes for patients with COPD, there is a strong rationale for introducing new, mechanism-based treatments into the COPD treatment pathway.

The cost-effectiveness analysis demonstrates the potential for mepolizumab to be a well-tolerated, cost-effective addition to existing SoC in the NHS, with three large, robust clinical trials demonstrating a significant reduction in exacerbations for patients receiving mepolizumab vs. SoC. The cost-comparison analysis showed mepolizumab to also be a less costly alternative when compared to dupilumab’s list price.

Company evidence submission for mepolizumab for treating chronic obstructive pulmonary disease with an eosinophilic phenotype [ID1237]

The introduction of mepolizumab to the treatment pathway would reduce the significant clinical, quality of life, and economic burden of COPD in the UK and provide patients with a treatment option that will lead to meaningful improvements in health.

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Company evidence submission for mepolizumab for treating chronic obstructive pulmonary disease with an eosinophilic phenotype [ID1237]

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Company evidence submission for mepolizumab for treating chronic obstructive pulmonary disease with an eosinophilic phenotype [ID1237]

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Appendices

- Appendix A: Summary of product characteristics (SmPC) and UK public assessment report
- Appendix B: Identification, selection and synthesis of clinical evidence
- Appendix C: Subgroup analysis
- Appendix D: Adverse reactions
- Appendix E: Published cost-effectiveness studies
- Appendix F: Health-related quality-of-life studies
- Appendix G: Cost and healthcare resource identification, measurement and valuation
- Appendix H: Clinical outcomes and disaggregated results from the model
- Appendix I: Price details of treatments included in the submission
- Appendix J: Supplementary clinical effectiveness evidence
- Appendix K: ITC/MAIC supplementary appendix

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Single technology appraisal

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

Summary of Information for Patients (SIP)

5 November 2025

File name	Version	Contains confidential information	Date
ID1237_Mepolizumab _COPD_SIP [noCON].docx	1	No	5 November 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the [Health Technology Assessment International – Patient & Citizens Involvement Group](#) (HTAi PCIG). Information about the development is available in an open-access [IJTAHC journal article](#)

SECTION 1: Submission summary

Note to those filling out the template: Please complete the template using plain language, taking time to explain all scientific terminology. Do not delete the grey text included in each section of this template as you move through drafting because it might be a useful reference for patient reviewers. Additional prompts for the company have been in red text to further advise on the type of information which may be most relevant and the level of detail needed. You may delete the red text.

1a) Name of the medicine (generic and brand name):

Mepolizumab (Nucala®)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Mepolizumab is intended for use in adults with uncontrolled chronic obstructive pulmonary disease (COPD) who continue to have frequent flare-ups (also called exacerbations) despite taking regular inhaled medicines.

A flare-up (or exacerbation) is a sudden worsening of breathing problems that goes beyond normal day-to-day variation and may need extra treatment, such as antibiotics, steroid tablets, or hospital care.

Specifically, mepolizumab is for people who have had two or more moderate exacerbations (meaning they needed antibiotics or steroid tablets) or at least one severe exacerbation (they required hospital care) within the past 12 months. People should also have a type of COPD called eosinophilic COPD, meaning their disease is linked to high levels of eosinophils (white blood cells involved in inflammation). Namely, this refers to people with blood eosinophil counts of 300 cells per microlitre or higher. This inflammation increases the risk of flare-ups.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Mepolizumab does not yet have marketing authorisation for the indication in this submission. A regulatory submission was made to the Medicines and Healthcare Products Regulatory Agency in 02/2025 via the national procedure route, with approval expected 01/2026. Committee for Medicinal Products for Human Use positive opinion is expected 01/2026, and European regulatory approval in 03/2026. Mepolizumab is already approved for this indication by the United States Food and Drug Administration (1).

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

2025

- Asthma + Lung UK representative contributed on a zero-fee basis to an NHS Confed Podcast. On the same basis an Asthma + Lung representative will also contribute to a Health on the Line podcast to be recorded in 2025.
- Asthma + Lung UK representative attended on a zero-fee basis a Parliamentary roundtable on prevention.
- Asthma + Lung UK representative attended on a zero-fee basis a GSK all staff conference as a speaker.

2024

- £55,000 – GSK provided a grant to support the Taskforce for Lung Health 2025 activities.
- £7,776 – GSK provided a fee for service to Asthma + Lung UK for input in the GSK severe asthma patient survey.
- £1,000 – GSK provided funding to Asthma + Lung UK towards the cost of helping people with lung disease, as part of the GSK IMPACT Awards programme.

2023

- £55,000 – GSK provided funding to support the Taskforce for Lung Health activities 2024.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Summary of information for patients for mepolizumab for treatment of uncontrolled chronic obstructive pulmonary disease with an eosinophilic phenotype [ID1237]

COPD and the impact of living with the condition

COPD refers to a group of lung conditions that cause breathing difficulties, including conditions such as chronic bronchitis (long-term airway inflammation) and emphysema (damage to the air sacs in the lungs) (2). COPD is characterised by persistent airway obstruction, causing breathlessness, chronic (long-term) cough, mucus production, wheezing and chest tightness, as well as tiredness and weight loss (3). The condition gradually worsens over time (4), making it harder to breathe and leading to tiredness, weight loss, and reduced quality of life (5, 6). People with COPD may also experience exacerbations, which are a sudden worsening of symptoms i.e. flare-ups that often need extra treatment, such as antibiotics, steroid tablets, or hospital care (7-9). They also cause the disease to worsen and increase the risk of having future flare-ups (9). COPD is also linked with many other health problems (known as co-morbidities). The ongoing inflammation in COPD can trigger or worsen co-morbidities such as heart disease, heart failure, brittle bones (osteoporosis), certain types of anaemia, lung cancer, depression, diabetes, and acid reflux (10, 11). These additional conditions often lead to more hospital visits, higher risk of death and increased healthcare costs.

In some people, COPD is linked to Type 2 inflammation which is caused by certain immune cells called eosinophils. High levels of eosinophils in the lungs can lead to more inflammation, making flare-ups and recurrent flare-ups more likely (12-16), and lead to persistent symptoms and lower quality of life, with recovery often prolonged (11, 17, 18). Research has shown that people with higher eosinophil levels may respond better to targeted treatments that reduce this inflammation, such as biologic medicines (11). Benefits from targeted biologic treatments begin to appear in people with eosinophil levels of 150 cells per microlitre or more (19-22), with stronger effects seen in those with levels of 300 cells per microliter or more (19-22).

Importantly, COPD does not just affect the person living with the disease, but also places a heavy burden on their caregivers, who experience significant emotional, physical, social, and financial burden, often reporting depression, anxiety, tiredness, social isolation, and lack of preparedness to manage symptoms or exacerbations (23).

How many people live with the condition?

In 2024/2025, 1,207,974 people had a recorded diagnosis of COPD in primary care in England, representing approximately 1.89% of the total population (24). Another large study, based on health records in England, found that in 2019 about 1 in 20 adults aged 40 and over had been diagnosed with COPD, and that the number of people with the condition has been steadily rising over the past 20 years (25). The study also estimated that around half a million people in England had COPD but had not been diagnosed yet.

It is estimated that up to 40% of people with COPD have Type 2 inflammation (26-30).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

COPD diagnosis is considered based on the presence of risk factors (such as smoking or exposure to air pollutants or chemical fumes) and symptoms including persistent or episodic shortness of breath that has become worse over time and is particularly noticeable during exercise, recurrent wheeze, a long-term cough that may be intermittent and/or produce mucus, and frequent chest infections (11, 31). Spirometry (a breathing test) may also be used to measure how well the lungs work.

Summary of information for patients for mepolizumab for treatment of uncontrolled chronic obstructive pulmonary disease with an eosinophilic phenotype [ID1237]

The level of eosinophils in the blood (called blood eosinophil count) is recognised as a marker of Type 2 inflammation (11), so can be used to identify people with eosinophilic COPD. Blood eosinophil count is widely available and routinely used in UK clinical practice to guide treatment escalation in COPD (31); therefore, this threshold is used to define the target population in this submission.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
 - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
 - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

In England, care for people with COPD is delivered by different parts of the healthcare system, including GP practices, hospitals, and community services. Treatment follows the national NICE guideline NG115 (31), which outlines a step-by-step approach to care based on how severe a person's symptoms are, how often they have flare ups (known as exacerbations), and whether they have signs of inflammation involving eosinophils, the type of white blood cells linked to lung inflammation. The Global Initiative for Chronic Obstructive Lung disease (GOLD) 2025 report framework is also widely used in clinical practice (11), and is in line with NG115 (31).

Before starting medicines and while using them, NICE recommends that everyone with COPD receives support to stop smoking, annual flu and pneumonia vaccinations, and access to pulmonary rehabilitation (an exercise and education programme to help manage breathlessness) (31). People should also receive advice on self-management and care for other health conditions linked to COPD. However, not everyone who could benefit from these services receives them (32).

The main treatments for COPD are inhaled medicines, which help open up the airways and reduce inflammation. If symptoms or exacerbations continue, treatments are gradually increased from short-acting inhalers for quick relief, to longer-acting inhalers, and then to triple therapy which combines three types of inhalers. Triple therapy is recommended for people who continue to have troublesome symptoms or frequent flare-ups despite other treatments.

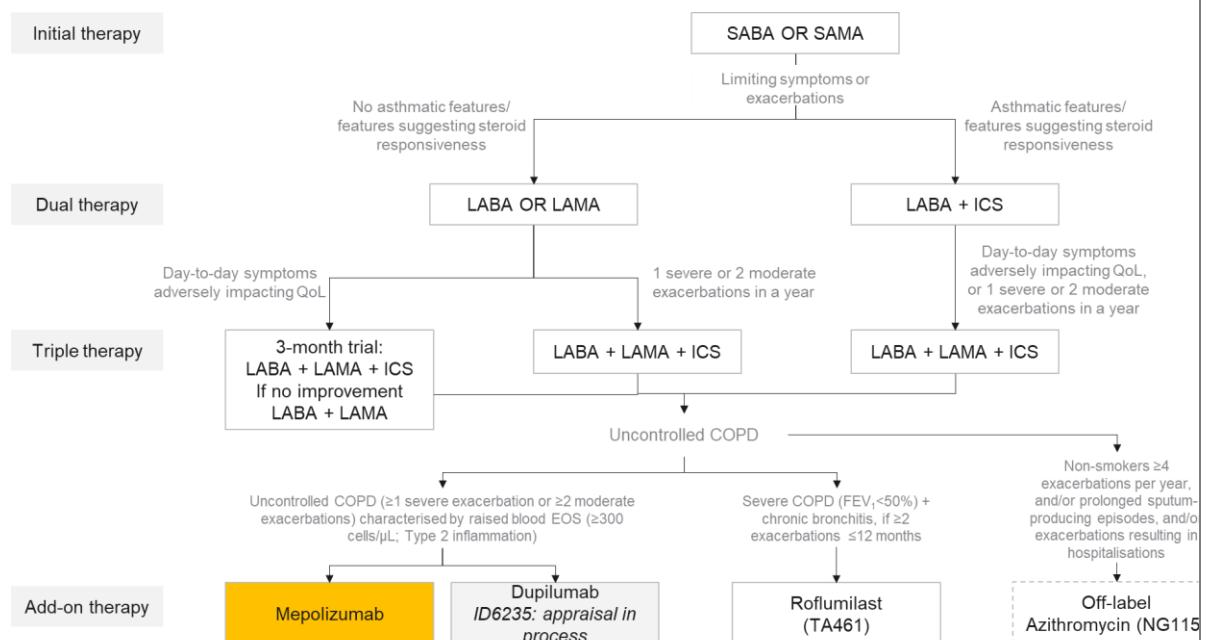
For those who still have exacerbations, despite taking triple therapy, there are very few additional treatment options. Roflumilast can be prescribed for people with severe COPD and chronic bronchitis, but it is rarely used due to side effects such as diarrhoea, nausea, and mood change (33, 34). According to NICE guidelines, the antibiotic, azithromycin, can be used in some people with COPD who no longer smoke and who keep having flare-ups despite treatment (31), but this use is not part of the medicine's UK licence. The GOLD report mentions it only for people with low eosinophil levels (less than 100 cells per microlitre) (11).

Dupilumab, a biologic medicine, is currently undergoing appraisal by NICE, with guidance expected to be published soon. It is being considered as an add-on maintenance treatment for people with uncontrolled COPD who have raised levels of eosinophils (the white blood cells linked to inflammation) (35). Studies of dupilumab have focused on people with chronic bronchitis (long-term inflammation of the airways) and moderate to severe disease (36, 37).

Mepolizumab is expected to be used in a similar group of adults with uncontrolled COPD linked to high levels of eosinophils (300 cells per microlitre or more) who continue to have two or more moderate or at least one severe flare-up each year despite taking triple therapy (Figure 1). Studies of mepolizumab have included people with eosinophilic COPD at different stages of the disease and with various types of lung changes, such as chronic bronchitis, and emphysema (damage to the air sacs in the lungs) (21, 38).

Both medicines target Type 2 inflammation, but they act on different parts of the inflammatory pathway to reduce exacerbations. As Type 2 inflammation varies from person-to-person, and many people with COPD continue to have flare-ups despite the availability of inhaled treatments, there is an ongoing need for a range of treatment options to manage COPD more effectively.

Figure 1: Future anticipated treatment pathway for COPD with mepolizumab



Source: NICE NG115 (31); NICE TA461 (33); NICE ID6235 GID-TA11246 (35).

Abbreviations: COPD, chronic obstructive pulmonary disease; EOS, eosinophils; FEV1, forced expiratory volume in 1 second; ICS, Inhaled corticosteroids; LABA, long-acting beta2- agonist; LAMA, long-acting muscarinic antagonist; NG, NICE Guideline; NICE, National Institute for Health and Care Excellence; QoL, Quality of life; SABA, short-acting beta2- agonist; SAMA, short-acting muscarinic antagonist TA, technology appraisal.

†GOLD categorises the severity of COPD into four grades based on spirometry (breathing test) results and symptom assessment, with 1 being mild, 2 moderate, 3 severe and 4 very severe.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the

Summary of information for patients for mepolizumab for treatment of uncontrolled chronic obstructive pulmonary disease with an eosinophilic phenotype [ID1237]

medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

The UK COPD voices report ran an 8-week consultation between September and November 2024 across seven different regions of the UK. Through group workshops (both in person or online) and individual interviews lasting 60–90 minutes, it gathered the views and experiences of 120 people living with COPD and their families (39).

Personal stories highlighted the significant impact of the disease on daily life. One person described *“the breathlessness attack was horrific. I wanted to die, I just wanted it to end and be over with”*. Another said, *“I once heard someone say it took them an hour and a half to get up and dressed in a morning. I thought that was an exaggeration and not possible, but that’s me now!”*.

The report also identified unequal access to healthcare and called for more joined-up, person-centred care (39). Many participants wanted better support to manage flare-ups at home, with faster access to treatment when needed, to help avoid hospital admissions and improve quality of life. There was also a clear interest in gaining access to new and innovative treatments. Another study explored what people with COPD value most in their treatment (including people from the UK, US, and Germany). Most participants would consider a switch in medication, mainly for improved efficacy, but also to reduce how often they need to take their medication (40). In addition, some people may face barriers to attending healthcare appointments, including psychosocial and practical challenges (41). Reducing how often treatment is needed could help ease these challenges and support those who find it difficult to engage regularly with healthcare services.

The UK COPD Voices report, which gathered views from people affected by COPD across the UK, also showed the heavy impact the condition has on family members and caregivers. Many described their caring role affected their relationships, work, finances, and personal time (39). Around half of caregivers provided 50 hours or more of care a week, and most were over the age of 65 and living with their own long-term conditions, such as diabetes and heart disease, leaving little time to look after their own health. Financial pressures were also raised; caregivers reported falling into debt or cutting back on activities that improve their own health and wellbeing (39).

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Summary of information for patients for mepolizumab for treatment of uncontrolled chronic obstructive pulmonary disease with an eosinophilic phenotype [ID1237]

Mepolizumab is a humanised monoclonal antibody, which means it is designed to target a specific substance in the body, in this case a protein called IL-5 (42). IL-5 binds to eosinophils triggering their growth, activation, survival and recruitment to the lungs, where they cause inflammation. Mepolizumab works by binding strongly and accurately to IL-5, blocking it from binding to eosinophils, and therefore stopping the signal that would usually help the eosinophils to grow and survive, reducing their production and survival (43). In addition, it is thought that blocking IL-5 also helps to inhibit direct and indirect effects of other IL-5 induced responses that may contribute to the disease or symptoms in other types of lung cells, including those lining the airways, muscle cells, and other immune cells (42). Mepolizumab is the first medicine to be appraised by NICE that targets IL-5 for the treatment of COPD.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Mepolizumab is intended to be used as add-on maintenance treatment to current standard of care (triple therapy; an inhaled corticosteroid [ICS], long-acting beta₂ agonist [LABA] and long-acting muscarinic antagonist [LAMA]). Inhaled corticosteroids aim to reduce swelling in the airways, long-acting beta₂ agonists relax the muscles around the airway, and long-acting muscarinic antagonists are used to widen the airway. Triple therapy can be prescribed as a single inhaler which delivers all three drugs in one dose or as multiple inhalers which deliver separate doses of each drug. The most common side effects of triple therapy include headache, back pain, a change in taste, diarrhoea, cough, throat pain and stomach flu (44).

The addition of mepolizumab is intended to help reduce Type 2 inflammation through the IL-5 pathway, synergising with the effects of the inhaled corticosteroid to further amplify the inflammation reduction needed in people whose disease remains uncontrolled, despite being on optimal triple therapy.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Mepolizumab is administered as an injection just beneath the skin every 4 weeks, as an add-on to current standard of care (triple therapy). Mepolizumab offers less frequent dosing compared with dupilumab, another add-on biologic agent, which is currently under NICE review and could receive published guidance shortly (35). Dupilumab is given every 2 weeks. Less frequent dosing with mepolizumab may reduce treatment burden and align better with people's preferences, which in turn can support adherence (taking medication as prescribed) and persistence (remaining on therapy) (45). Lowered frequency of use is a preferred feature among people with COPD (40), and improved adherence is particularly important in COPD, where other health conditions that occur alongside COPD and polypharmacy (need for multiple medications) already contributes to high treatment burden (46).

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The clinical trial programme providing evidence for mepolizumab in people with COPD with Type 2 inflammation, characterised by blood eosinophil count, includes three Phase 3 trials called MATINEE, METREX, and METREO. In all studies, people received mepolizumab at a dose of 100 mg every 4 weeks (the same dose being assessed by NICE) in combination with triple therapy[†].

MATINEE ([NCT04133909](#))

The MATINEE trial (38) was an international clinical study carried out across multiple hospitals in Asia, Europe (including the UK), Eastern Europe, North America, and other regions. The study was randomised, placebo-controlled, and double-blind, meaning participants were randomly assigned to receive either mepolizumab or a placebo (a dummy treatment), and neither they nor the researchers knew which treatment they were receiving. The trial finished in August 2024.

People could take part if they had Type 2 inflammation, identified by high levels of eosinophils (300 cells per microlitre or more at screening [i.e. the time at which they are assessed for suitability to join the study] and 150 cells per microlitre or more within the past 12 months) and had experienced two or more moderate flare-ups or at least one severe flare-up in the previous year. The MATINEE study included people who represent the same group considered in this NICE appraisal.

People received either mepolizumab or placebo (a dummy treatment) every 4 weeks for between 52 and 104 weeks, in addition to triple inhaled therapy. A total of 804 people took part in the study, with 403 receiving mepolizumab and 401 receiving placebo.

This study looked at how well mepolizumab worked in a broad group of people with COPD, including those with chronic bronchitis (long-term inflammation of the airways), emphysema (damage to the air sacs in the lungs), and different levels of disease severity. It was also the first trial to study the long-term effects of a biologic treatment in COPD, lasting up to 2 years, and to include a planned analysis of hospital admissions and emergency department visits, which are key priorities for improving outcomes for people with COPD and for the healthcare system.

METREX ([NCT02105948](#)), and METREO ([NCT02105961](#))

The METREX and METREO studies (21) were international clinical trials that, like MATINEE, were randomised, double-blind, and placebo-controlled, meaning participants were randomly assigned

Summary of information for patients for mepolizumab for treatment of uncontrolled chronic obstructive pulmonary disease with an eosinophilic phenotype [ID1237]

to receive either mepolizumab or a placebo (a dummy treatment), and neither they nor the researchers knew which treatment they were receiving. Both trials ran for 52 weeks.

The METREX study included people with COPD who had two or more moderate or at least one severe flare-up in the past year despite triple inhaled therapy. People were grouped by levels of eosinophils into a high group (150 cells per microlitre or more at screening or 300 cells per microlitre or more in the past year) and a low group (below these levels).

The METREO study had similar criteria but included only those in the high eosinophil group. In both studies, people were randomly given mepolizumab 100 mg, mepolizumab 300 mg[†], or a placebo (dummy treatment) by injection every 4 weeks for 1 year.

The trials also included a group of people with levels of eosinophils of 300 cells per microlitre or more at the start of the study. This group is referred to as the modified intention-to-treat (mITT-300) population.

Pooled analysis: MATINEE ([NCT04133909](#)), METREX ([NCT02105948](#)), and METREO ([NCT02105961](#))

A combined analysis of data from the METREX, METREO, and MATINEE studies was carried out, including everyone with a level of eosinophils of 300 cells per microlitre or more. Data from MATINEE and the modified intention-to-treat (mITT-300) groups from METREX, and METREO were brought together to form what is known as the pooled mITT-300 population (47).

[†]METREX also included a mepolizumab 300 mg arm, however this dose is not relevant for COPD and therefore is not presented in the submission.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Efficacy from the clinical trials

In the Phase 3 trials, the primary endpoint was the annualised rate of moderate and severe exacerbations, which is a clinically meaningful measure of treatment impact as it captures the key driver of disease progression (exacerbations).

MATINEE

In MATINEE, mepolizumab significantly reduced the annualised rate of moderate/severe exacerbations by 21% compared with placebo. It also significantly delayed the time-to-first moderate/severe exacerbations by 98 days vs. placebo, and decreased the chance of a moderate/severe exacerbation event by 23% (38, 48). The effect was sustained for up to 2 years.

Importantly, 35% of people had fewer emergency visits or hospitalisations due to exacerbations annually compared with placebo, up to Week 104 (nominally significant[†]).

Exacerbations were consistently reduced in subgroups regardless of airflow obstruction, type of COPD (chronic bronchitis or emphysema), varying treatment durations, cardiovascular comorbidities, prior severe exacerbations, and duration of COPD disease (38, 48).

Pooled mITT-300 analysis (MATINEE, METREX and METREO)

Similar to MATINEE, in all individuals with a blood eosinophil count of 300 cells per microlitre or more across the three trials, mepolizumab significantly reduced the annualised rate of moderate/severe exacerbations by 21% vs. placebo and nominally[†] significantly reduced the rate of exacerbations requiring ED visit and/or hospitalisation by 29% (47).

Efficacy using trial data and statistical analyses

As there are no head-to-head clinical trials directly comparing mepolizumab with dupilumab, a form of statistical analyses called a matching-adjusted indirect comparison (MAIC) was performed. Using this method, data from the mepolizumab studies were adjusted to match the characteristics of people in the dupilumab studies. Note, the dupilumab studies only enrolled people with chronic bronchitis and moderate-to-severe COPD, while the mepolizumab trials enrolled people with moderate-to-very severe disease and all types of COPD, not just chronic bronchitis. Because the disease can appear differently in different people, there were two definitions of chronic bronchitis used for the mepolizumab trials, to ensure different aspects of the disease were captured; one was investigator-defined, relying on clinical judgement of the study investigators, and one based on the St. George's Respiratory Questionnaire for COPD (SGRQ-C), which is a validated patient reported outcome tool.

The matching-adjusted indirect comparison found no statistically significant differences in the overall rate of moderate/severe exacerbations (49), however across several exacerbation outcomes, the estimated exacerbation rates were either lower or similar for mepolizumab compared with dupilumab. In people with investigator-defined chronic bronchitis (long-term inflammation of the airways), mepolizumab was associated with a lower yearly rate of moderate/severe exacerbations and severe exacerbations (49). When chronic bronchitis was defined by SGRQ-C, results were comparable between treatments. The time before a first moderate/severe exacerbation was longer with mepolizumab compared to dupilumab under both definitions of chronic bronchitis (49).

Whilst the MAIC analysed a restricted population from the mepolizumab trials to match the population of the dupilumab trials, mepolizumab also demonstrated efficacy in subgroups that were not evaluated in the dupilumab trials (36, 37) e.g. people without chronic bronchitis (50) and those with very severe disease [GOLD 4] (51)). In addition, the rate of exacerbations requiring emergency department visits and/or hospitalisation could not be included in the MAIC as this outcome was not initially analysed in the dupilumab trials. Further analyses from the MATINEE study showed that mepolizumab helped reduce exacerbations that led to hospital stays or emergency room visits vs. placebo, suggesting it may help ease the burden of COPD on both affected individuals and the healthcare system (52).

[†]Nominally significant means that the result meets the statistical threshold to be considered meaningful (i.e. a p-value <0.05), however it has not been tested against stricter, pre-defined rules that account for testing many outcomes at once.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as patient reported outcomes (PROs).

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Summary of information for patients for mepolizumab for treatment of uncontrolled chronic obstructive pulmonary disease with an eosinophilic phenotype [ID1237]

Quality of life was measured in the mepolizumab clinical trials using a number of different measures:

- EQ-5D-5L: A questionnaire used to assess five areas: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression
- COPD Assessment Test (CAT) score: a validated, patient-completed questionnaire consisting of 8 items that assess the impact of COPD on a person's daily life, with a total score for 0–40, where higher score indicates greater impairment
- SGRQ: a questionnaire with 50 questions asking people with COPD about their symptoms, daily activities, and impact on life with a total score from 0–100, with 100 being the worst possible health status.
- Evaluating Respiratory Symptoms (E-RS) COPD: Includes 11 respiratory symptom items, providing the RS-total score, and three subscale scores for breathlessness, cough and sputum, and chest symptoms.

Results

MATINEE

Mepolizumab demonstrated an improvement in quality of life from baseline, measured by the SGRQ, which was numerically higher than placebo. Across the different health-related quality of life measurements taken, high rates of responders were assessed in the mepolizumab-treated group, however there was no statistically significant difference observed between mepolizumab and placebo-treated people with respect to the responder analyses. However, in a post-hoc analysis (an analysis performed after the study was completed that was not originally planned) of people with moderate-to-severe disease (GOLD stage 2–3), mepolizumab demonstrated a statistically significant improvement in SGRQ scores compared with placebo (odds ratio: 1.58 [95% CI 1.01, 2.48]) (51).

Pooled mITT-300 analysis

In the pooled trial analysis, a statistically significant improvement in SGRQ-C score from baseline was observed for mepolizumab compared to placebo (47).

MAIC vs. dupilumab

There was no statistically significant difference between mepolizumab and dupilumab in the health-related quality of life outcomes tested.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Mepolizumab has an established safety profile and is a well-tolerated treatment across approved indications, studied for up to 10 years in both clinical trials and in the real world. In the COPD trials, the safety of mepolizumab is consistent with its known benefit:risk profile.

In MATINEE, the overall incidence and event rate of on-treatment adverse events, serious adverse events, and adverse events of special interest were similar between the mepolizumab and placebo groups. The overall incidence of on-treatment adverse events considered by the investigator to be related to study treatment was similar between the treatment groups (5% in mepolizumab, 4% in placebo). AEs leading to treatment discontinuation were also similar between the two treatment arms (3% in mepolizumab, 4% in placebo). The most frequently reported on-treatment adverse events in both groups were exacerbation or worsening of COPD, COVID-19, nasopharyngitis [common cold], headache, and pneumonia (38). The most common serious adverse events were exacerbation or worsening of COPD (mepolizumab: 11% and placebo: 14%) and pneumonia (3% in both arms). Death during or after the treatment period occurred in 11 people (3%) in each treatment group (mepolizumab and placebo). None of these deaths were thought to be related to the study treatment by the investigator.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

As described in response to 2a, people with Type 2 inflammation, indicating eosinophilic COPD, have an increased risk of exacerbations, and a lower quality of life. Prevention of exacerbations is key for the successful management of COPD, as they increase the likelihood of hospitalisation, cardiovascular events, future exacerbations, disease progression and death.

Mepolizumab offers a targeted anti-IL-5 therapy for people with uncontrolled eosinophilic COPD on optimised inhaled triple therapy, a population with limited treatment options. Results from the key clinical trial, MATINEE, supported by the pooled mITT-300 analysis, provide a robust evidence base demonstrating the efficacy and safety of mepolizumab for these people. The matching-adjusted indirect comparison (MAIC) vs. dupilumab showed no statistically significant differences in overlapping populations but numerically favourable trends in some key exacerbation outcomes for mepolizumab (Section 3e). Moreover, mepolizumab has demonstrated benefit vs. placebo in subgroups of people who were not enrolled in the dupilumab trials (i.e. people without chronic bronchitis, very severe disease [GOLD level 4], and people with a blood eosinophil count of less than 300 cells per microlitre). The numerical trends observed in the MAIC as well as the benefits in the additional subgroups suggest that mepolizumab may offer at least similar or greater health benefits vs. dupilumab, and efficacy in a broader population of people with COPD. Mepolizumab is administered every 4 weeks, which may be less burdensome than the dupilumab 2-weekly dosing schedule, and align with people's preferences and improve adherence and persistence to treatment (Section 3c).

Finally, reductions in flare-ups may help to alleviate the high burden to caregivers. Notably, the significant reduction in hospitalisations and emergency department visits with mepolizumab

further highlights the potential benefit for mepolizumab for people with COPD, caregivers, and health systems by avoiding this outcome.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments.

Triple therapy is administered by inhaler, while mepolizumab is given by injection just under the skin. Some people may be uncomfortable with injections due to a fear of needles or may prefer oral or inhaled options. Adding a treatment with a different mode of administration which does not provide immediate symptom relief, may be seen as an additional burden by some people, particularly if they are used to inhaled medicines. People also need to receive initial training on how to self-administer mepolizumab.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

The economic analysis looked at adults with COPD and raised blood eosinophils (an eosinophilic phenotype) whose disease remained uncontrolled (≥ 2 moderate or ≥ 1 severe exacerbations within 12 months) despite using inhaled triple therapy. The economic model compares mepolizumab with background therapy, and with dupilumab.

How the health economic model reflects the condition

The model was built in Excel and followed people over their lifetime to estimate how COPD flare-ups (exacerbations) affect health outcomes, quality of life, and NHS costs. The main treatment goal was to reduce exacerbations, as these have the biggest effect on people's survival and quality of life, as well as costs to the NHS. The model included different health states defined by the severity of exacerbations (moderate or severe), to capture their short- and long-term impact on health, costs, and future risk of further exacerbations. It also accounted for some people stopping treatment over time.

Modelling how much a treatment extends life

COPD is a leading cause of death in the UK, with severe exacerbations being a major cause among people with COPD. Exacerbations also increase the risk of future flare ups. The model estimated the likelihood of death in each health state, with a higher risk following severe exacerbations.

Modelling how much a treatment improves quality of life

Quality of life data from the mepolizumab trials were used to calculate how COPD affects a person's overall health and wellbeing, following NICE guidance (53, 54). These data were used to estimate utility values, which are numerical scores that reflect how good or bad someone's health is. The utility values were also adjusted for age (to reflect the decrease in quality of life as individuals get older).

People often feel worse after an exacerbation, so lower utility values were assigned after an exacerbation had occurred, depending on the severity and time since the event. These were used to estimate quality-adjusted life years, which combine how long someone lives (their total life years) with their quality of life during that time. This helps compare the overall benefits of different treatments.

Modelling how the costs of treatment differ with the new treatment

The model accounts for the costs of treating and managing COPD exacerbations across a person's lifetime. This included costs of treatment, management of COPD and management of exacerbation events. Both mepolizumab and dupilumab were assumed to be self-administered injections in 95% of people, with a one-off cost for training at the start of the model. Side effects were not expected to differ between treatments; therefore, no additional adverse event costs were included. Disease management and costs per exacerbation were assumed to be the same between standard of care, mepolizumab and dupilumab.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Mepolizumab is the first targeted anti-IL-5 therapy for people with uncontrolled eosinophilic COPD on maximal inhaled triple therapy; a population with limited treatment options.

Quality-adjusted life year benefits not captured in the quality-adjusted life year calculation

COPD has a greater impact on people from lower-income or disadvantaged backgrounds, who are more likely to experience exacerbations and need hospital treatment (55, 56). Mepolizumab offers a well-tolerated and effective option, with up to 95% of people potentially being able to self-administer, which may help reduce barriers such as travel costs, time off work, and difficulties accessing healthcare. As noted in Section 3c, having a treatment that is easier to use and requires less frequent dosing could also help people stay on treatment, reduce treatment burden, and support caregivers and health services by preventing complications and lowering the number of medicines needed (40, 45, 46). Together, these factors support caregivers, lessen pressure on healthcare services, and help to reduce inequalities in COPD care.

Exacerbations make COPD worse over time and increase the risk of hospital admissions, heart problems, future exacerbations, and even death. They also represent a major cost to the NHS. The annual cost of treating moderate/severe exacerbations is expected to rise from about £0.6 billion in 2011 to more than £1 billion by 2030 (57). Most of these costs come from hospital stays and emergency department visits (31, 58-60). Recent UK data also highlight the continuing impact of these events on healthcare use, with hospital and emergency department visits making up most COPD-related costs in the 6 months following an acute exacerbation (60). The substantial direct costs of treating people with moderate-to-severe COPD increases with exacerbation severity (61, 62). Introducing effective, self-administered treatments such as mepolizumab could help to reduce the number of exacerbations which could therefore help ease pressure on the NHS, especially during winter when respiratory illnesses are most common (24).

COPD also places a heavy burden on caregivers (Section 2d), who often spend long hours providing support, sometimes while managing their own health problems. Fewer exacerbations could reduce this burden, helping caregivers maintain their own wellbeing.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

[Find more general information about the Equality Act and equalities issues here](#)

COPD disproportionately affects people living in deprived areas, where risk factors such as smoking, air pollution, and poor housing conditions are more common (63). People from socioeconomically disadvantaged backgrounds who also have multiple long-term health conditions are disproportionately affected by COPD and are at a higher risk of experiencing exacerbations and hospital admissions compared with the general population (55, 56). Those living in the most deprived 10% of households are more than 2.5 times more likely to have COPD than the most affluent 10% (32). People with fewer resources also tend to have more frequent flare-ups and less access to consistent, high-quality care (55, 64).

Access to specialist diagnosis and treatment is uneven across the UK, with many people needing to travel long distances for appointments and others experiencing delays or gaps in care (63). Some

Summary of information for patients for mepolizumab for treatment of uncontrolled chronic obstructive pulmonary disease with an eosinophilic phenotype [ID1237]

people face significant barriers to accessing specialist care services, often needing to travel long distances for treatment (63). Differences in the availability and quality of COPD services are influenced by factors such as where people live, rural location, ethnicity, and socioeconomic background (39). Some people also face social or practical barriers to attending appointments (41). Treatments that are easy to use and require less frequent dosing may help reduce this burden, improve adherence, and lessen healthcare inequalities.

Access to pulmonary rehabilitation (an exercise and education programme that helps people manage breathlessness) is another key part of care (65). However, many people report that this service is hard to access, with long waiting times or limited availability, especially for those whose first language is not English (39). In some areas, pulmonary rehabilitation is offered only once a year, while in others, it may not be available at all.

Digital exclusion is a major challenge in COPD care. Limited access to technology or low digital confidence can make it harder for some people, especially older adults, and those in rural or deprived areas, to use digital health tools such as online self-management programmes or remote monitoring. This can widen existing health inequalities (66, 67). While digital tools can improve self-management and early detection of flare-ups, their benefits are not shared equally. Inclusive design, affordable internet access, and support to build digital skills are needed to ensure new technologies reduce, rather than deepen, inequality (68).

The impact of a well-tolerated and effective treatment in reducing exacerbations on these people and on reducing inequalities should be considered.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.

Where possible, please provide open access materials or provide copies that patients can access.

Information relating to mepolizumab

- [MATINEE key study publication](#)
- [METREX, and METREO key study publication](#)

Information relating to COPD

- [NICE guideline NG115: Chronic obstructive pulmonary disease in over 16s: diagnosis and management](#)
- [2025 GOLD report](#)

Further information on NICE and the role of patients:

- [Public Involvement at NICE](#)
- [NICE's guides and templates for patient involvement in HTAs](#)
- [EUPATI guidance on patient involvement in NICE](#)
- [EFPIA – Working together with patient groups](#)
- [National Health Council Value Initiative](#)
- [INAHTA](#)

Summary of information for patients for mepolizumab for treatment of uncontrolled chronic obstructive pulmonary disease with an eosinophilic phenotype [ID1237]

- [European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe](#)

4b) Glossary of terms

Adverse event: Any undesirable experience associated with the use of a medical product in a patient. It may or may not be caused by the product. Adverse events may be mild, moderate, or severe.

Blood eosinophil count: A measure of the level of eosinophils in the blood. A level of 300 cells per microlitre or more is considered to be a marker of Type 2 inflammation (eosinophilic COPD).

Chronic obstructive pulmonary disease (COPD): A group of lung conditions that cause breathing difficulties, including conditions such as chronic bronchitis (long-term airway inflammation) and emphysema (damage to the air sacs in the lungs).

Clinical trial/clinical study: A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. They are carefully designed, reviewed, and completed, and need to be approved before they can start.

Efficacy: The measurement of a medicine's desired effect under ideal conditions, such as in a clinical trial.

Exacerbation: A sudden worsening of breathing problems, which goes beyond the normal day-to-day variation that may require extra treatment or medical attention.

EQ-5D-5L: A questionnaire used to assess five areas: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

Eosinophilic phenotype: A type of COPD characterised by high levels of eosinophils (a type of white blood cell), which causes inflammation in the lungs and means these people are at higher risk of exacerbations. Defined in the submission as blood eosinophil level of 300 cells per microlitre or more.

GOLD levels: Categorises the severity of COPD into four grades based on spirometry (breathing test) results and symptom assessment, with 1 being mild, 2 moderate, 3 severe and 4 very severe.

Matching-adjusted indirect comparison (MAIC): a statistical analysis method used to compare two treatments from different studies when no direct head-to-head data are available. It works by adjusting one study's participant data (in this case mepolizumab) to better match the characteristics of the people in another study (in this case dupilumab), so the results can be more fairly compared.

Quality-adjusted life year: A measure of disease burden that includes the length and quality of life.

Quality of life: A measure of the overall enjoyment and happiness of life including aspects of an individual's sense of well-being and ability to carry out activities of daily living.

Randomised: People were allocated at random to one of two groups.

Statistically significant: A statistically significant result means the findings are unlikely to be a result of chance, and show a 'real' difference.

Subcutaneous: Giving medicines through a needle inserted under the skin.

Type 2 inflammation: A type of immune response involving cells like eosinophils and cytokines such as IL-4, IL-5, and IL-13, which can lead to increased mucus production, airway damage, and more frequent exacerbations in people with COPD. Type 2 inflammation presents as eosinophilic COPD which is defined by blood eosinophil count of 300 cells per microlitre or more.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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Summary of information for patients for mepolizumab for treatment of uncontrolled chronic obstructive pulmonary disease with an eosinophilic phenotype [ID1237]

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Table 1: Baseline characteristics in combined BOREAS/NOTUS trials and restricted populations of the MATINEE mITT trial

Characteristic	Combined BOREAS / NOTUS trials		Restricted population of MATINEE mITT trial – defining CB based on investigator assessment		Restricted population of MATINEE mITT trial after matching – defining CB based on investigator assessment – after MAIC	
	Dupilumab (N = 938)	PBO (N = 936)	Mepo (N = ■■■)	Mepo (N = ■■■)	Mepo (ESS = ■■)	PBO (ESS = ■■■)
Age, Mean (SD)	65.1 (8.0)	65.0 (8.3)	■■■■■	■■■■■	■■■■■	■■■■■
Female, n (%)	320 (34.1%)	302 (32.3%)	■■■■■	■■■■■	■■■	■■■
Male, n (%)	618 (65.9%)	634 (67.7%)	■■■■■	■■■■■	■■■	■■■
Not White, n (%)	123 (13.1%)	123 (13.1%)	■■■■■	■■■■■	■■■	■■■
White, n (%)	815 (86.9%)	813 (86.9%)	■■■■■	■■■■■	■■■	■■■
Asia, n (%)	67 (7.1%)	66 (7.1%)	■■■■■	■■■■■	■■■	■■■
East Europe, n (%)	361 (38.5%)	358 (38.2%)	■■■■■	■■■■■	■■■	■■■
Latin America, n (%)	255 (27.2%)	256 (27.4%)	■■■■■	■■■■■	■■■	■■■
Western Countries/High-income, n (%)	255 (27.2%)	256 (27.3%)	■■■■■	■■■■■	■■■	■■■
BMI < 25, n (%)	315 (33.6%)	317 (33.9%)	■■■■■	■■■■■	■■■	■■■
BMI 25 to < 30, n (%)	332 (35.4%)	352 (37.6%)	■■■■■	■■■■■	■■■	■■■
BMI ≥ 30, n (%)	291 (31.0%)	267 (28.5%)	■■■■■	■■■■■	■■■	■■■
Duration of COPD (years), Mean (SD)	–	–	■■■■■	■■■■■	■■■■■	■■■■■
Mod/Severe exacerbations, Mean (SD)	2.2 (1.0)	2.2 (0.9)	■■■■■	■■■■■	■■■■■	■■■■■

Characteristic	Combined BOREAS / NOTUS trials		Restricted population of MATINEE mITT trial – defining CB based on investigator assessment		Restricted population of MATINEE mITT trial after matching – defining CB based on investigator assessment – after MAIC	
	Dupilumab (N = 938)	PBO (N = 936)	Mepo (N = ■■■)	Mepo (N = ■■■)	Mepo (ESS = ■■)	PBO (ESS = ■■■)
Severe exacerbations = 0, n (%)	696 (74.2%)	722 (77.1%)	■■■■■	■■■■■	■■■	■■■
≥ 1, n (%)	242 (25.8%)	214 (22.9%)	■■■■■	■■■■■	■■■	■■■
Current smokers, n (%)	276 (29.4%)	282 (30.1%)	■■■■■	■■■■■	■■■	■■■
Former smokers, n (%)	662 (70.6%)	654 (69.9%)	■■■■■	■■■■■	■■■	■■■
Baseline blood eosinophil count (Mean, SD)	0.524 (0.31)	0.535 (0.33)	■■■■■	■■■■■	■■■■■	■■■■■
SGRQ-C total score at baseline (Mean, SD)	50.2 (17.4)	49.8 (17.2)	■■■■■	■■■■■	■■■■■	■■■■■
E-RS:COPD score at baseline (Mean, SD)	13.2 (6.95)	13.1 (7.05)	■■■■■	■■■■■	■■■■■	■■■■■

Source: Data on File (Matching-adjusted indirect comparison: final report) (166)

Abbreviations: BMI, body mass index; CB, chronic bronchitis; COPD, chronic obstructive pulmonary disorder; E-RS:COPD, Evaluating Respiratory Symptoms in COPD; ESS, effective sample size; mITT, modified intention to treat; NA, not applicable; SC, subcutaneous; SD, standard deviation; SGRQ-C, St. George's Respiratory Questionnaire – COPD specific version.

Table 2: Baseline characteristics in the combined BOREAS / NOTUS trials and restricted populations of the pooled MATINEE / METREO / METREX trials

Characteristic	Combined BOREAS / NOTUS trials		Restricted population of pooled MATINEE / METREO / METREX trials – defining CB based on SGRQ-C responses at baseline		Restricted population of pooled MATINEE / METREO / METREX trials after matching – defining CB based on SGRQ-C responses at baseline – After MAIC	
	Dupilumab (N = 938)	PBO (N = 936)	Mepo (N = [REDACTED])	PBO (N = [REDACTED])	Mepo N = [REDACTED]; ESS = [REDACTED])	PBO (N = [REDACTED]; ESS = [REDACTED])
Age (years), Mean (SD)	65.1 (8.0)	65.0 (8.3)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Female, n (%)	320 (34.1%)	302 (32.3%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Male, n (%)	618 (65.9%)	634 (67.7%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Race – Not White, n (%)	123 (13.1%)	123 (13.1%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Race – White, n (%)	815 (86.9%)	813 (86.9%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Geographic region – Asia	67 (7.1%)	66 (7.1%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
East Europe	361 (38.5%)	358 (38.2%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Latin America	255 (27.2%)	256 (27.4%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Western Countries/High-income	255 (27.2%)	256 (27.3%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
BMI < 25, n (%)	315 (33.6%)	317 (33.9%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
BMI 25 to <30, n (%)	332 (35.4%)	352 (37.6%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
BMI ≥ 30, n (%)	291 (31.0%)	267 (28.5%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Duration of COPD (years), mean (SD)	–	–	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Characteristic	Combined BOREAS / NOTUS trials		Restricted population of pooled MATINEE / METREO / METREX trials – defining CB based on SGRQ-C responses at baseline		Restricted population of pooled MATINEE / METREO / METREX trials after matching – defining CB based on SGRQ-C responses at baseline – After MAIC	
	Dupilumab (N = 938)	PBO (N = 936)	Mepo (N = ■■■)	PBO (N = ■■■)	Mepo N = ■■■; ESS = ■■■)	PBO (N = ■■■; ESS = ■■■)
Number of moderate/severe exacerbations, mean (SD)	2.2 (1.0)	2.2 (0.9)	■■■	■■■	■■■	■■■
Number of severe exacerbations at baseline, n (%)						
0	696 (74.2%)	722 (77.1%)	■■■	■■■	■■■	■■■
≥1	242 (25.8%)	214 (22.9%)	■■■	■■■	■■■	■■■
Smoking status, n (%)			■■■	■■■	■■■	■■■
Current smoker, n (%)	276 (29.4%)	282 (30.1%)	■■■	■■■	■■■	■■■
Former smoker, n (%)	662 (70.6%)	654 (69.9%)	■■■	■■■	■■■	■■■
Baseline BEC (Mean, SD)	0.524 (0.31)	0.535 (0.33)	■■■	■■■	■■■	■■■
SGRQ-C total score (Mean, SD)	50.2 (17.4)	49.8 (17.2)	■■■	■■■	■■■	■■■
E-RS:COPD score (Mean, SD)	13.2 (6.95)	13.1 (7.05)	■	■	■	■

Source: Data on File (Matching-adjusted indirect comparison: final report) (166)

Abbreviations: BEC, blood eosinophil count; BMI, body mass index; CB, chronic bronchitis; COPD, chronic obstructive pulmonary disorder; ERS:COPD, Evaluating Respiratory Symptoms in COPD; ESS, effective sample size; mITT, modified intention to treat; NA, not applicable; SC, subcutaneous; SD, standard deviation; SGRQ-C, St. George's Respiratory Questionnaire – COPD specific version.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Clarification questions

12 December 2025

File name	Version	Contains confidential information	Date
ID1237 mepolizumab clarification questions v2.0 [CON]	1	Yes	12 December 2025

Section A: Clarification on effectiveness data

Indirect Treatment Comparison (ITC)

A1. Company submission (CS), Section 2.10.5 (page 114). Please could the company clarify the approach used to identify and justify the selection of variables adjusted for in the matched-adjusted indirect comparison (MAIC)? Was clinical advice sought during this process?

The variables included in the matching-adjusted indirect comparison (MAIC) were selected based on the baseline characteristics reported in the published clinical trials of mepolizumab and dupilumab. These characteristics were used to inform the set of available variables for matching and reflect those consistently reported. An internal GSK pulmonologist was consulted to validate the selection of variables.

A2. The analyses conducted to compare trials with individual participant data (IPD) evidence (MATINEE, METREX, and METREO) and aggregate data (NOTUS and BOREAS) utilised a MAIC. However, a multilevel-network meta-regression (ML-NMR) would be more suitable.(1) It appears that adequate covariate data are available from the aggregate data trial for this method to be conducted. As this method does not need to reweight to match across studies, it will lead to increased sample sizes. This method is now accessible using the *multinma* package in R,(2) and is accepted by NICE (see TA1013).(3) Could the company update the analyses with this approach?

Multi-network meta regression (ML-NMR) models have been fitted for the primary endpoint as a supplementary analysis to the MAICs.

In alignment with the methodology applied in the MAICs, ML-NMR models were fitted for both populations:

- Population 1: Defining chronic bronchitis based on investigator assessment (using individual patient-level data [IPD] from the restricted population of the MATINEE trial, and aggregate data from the NOTUS and BOREAS trials)
- Population 2: Defining chronic bronchitis based on Saint George's Respiratory Questionnaire for COPD (SGRQ-C) responses at baseline (using IPD from

restricted populations of the MATINEE, METREX, and METREO trials, and aggregate data from the NOTUS and BOREAS trials).

With these three (for Population 1) or five (for Population 2) trials, a network linking studies through placebo as common comparator was established.

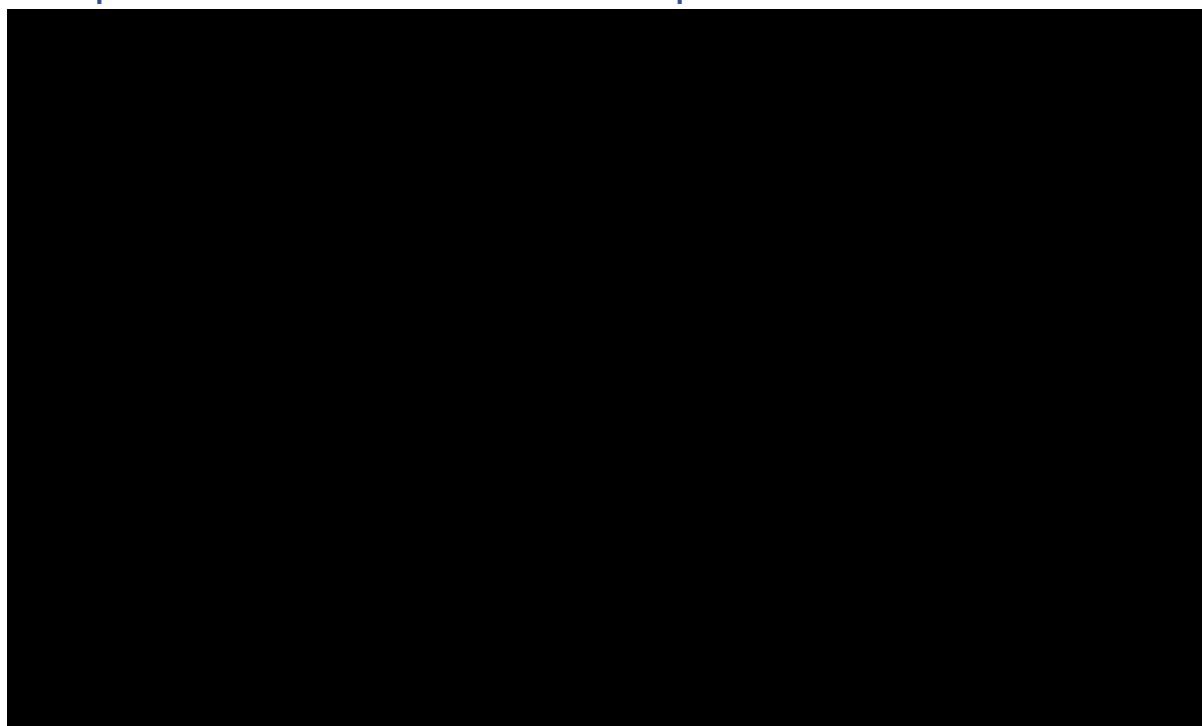
Rates were modelled using observed number of exacerbations and offset terms for each study. Since the negative binomial distribution is not implemented in the *multinma* package in R, the Poisson distribution was used for the underlying data generating model.

The same covariates as in the MAICs were included: Age (in years, numerical), Sex (categorical; male vs. female), Race (categorical; White vs. not White); Geographic region (categorical; Asia vs. Latin America vs. East Europe vs. Western Countries), Body Mass Index (categorical; $<25 \text{ kg/m}^2$ vs. ≥ 25 to $<30 \text{ kg/m}^2$ vs. $\geq 30 \text{ kg/m}^2$), Number of moderate/severe exacerbations at baseline (numerical), Severe exacerbations at baseline (categorical; 0 vs. ≥ 1), Smoking status (categorical; current vs. never/former), Blood eosinophil count at screening (numerical), SGRQ-C total score at baseline (numerical), evaluating respiratory symptoms in COPD (E-RS:COPD) score at baseline (numerical; not collected in METREO/METREX trials so included in the Population 1 analysis only). Covariates were standardised on a common scale to help convergence to the posterior distribution using the Markov Chain Monte Carlo (MCMC) method. The model was fitted using weak, non-informative priors.

As data for dupilumab was only available through aggregate study information and the network is small, we used the shared effect modifier assumption, which assumes that the impact (effect modification) of covariates on treatment effectiveness is the same for the dupilumab and mepolizumab trials in the network, allowing IPD and aggregate data to be synthesised.

Figure 1 summarises the results of the analysis performed for Population 1 and shows the estimated relative treatment effects (expressed as rate ratios on the log scale; with rate ratios and 95% credibility interval added to the right) of all pairs of treatments and in each of the three studies included. As a result of the shared effect modifier assumption, the estimated rate ratio of mepolizumab vs. dupilumab is the same across all studies.

Figure 1: RRs of number of moderate or severe exacerbations estimated from ML-NMR for all pairs of treatments and in all studies – Population 1



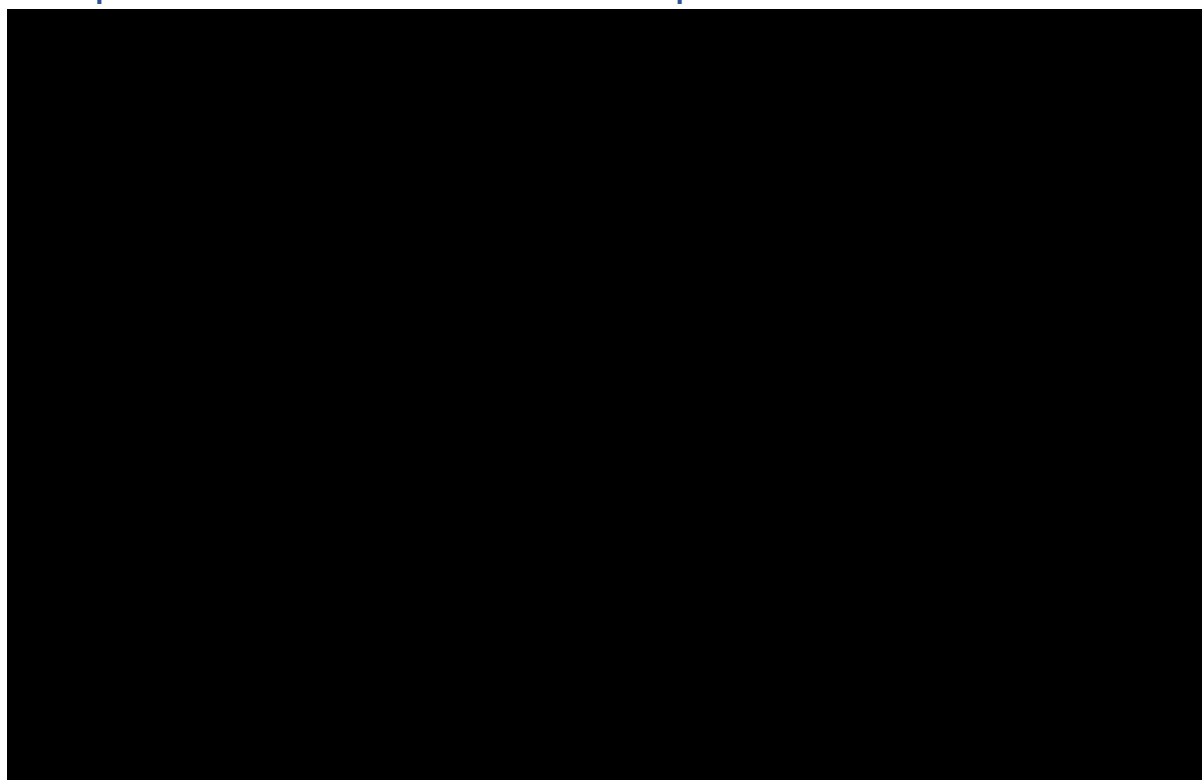
Abbreviations: ML-NMR, multi-level network meta-regression; RR, rate ratio.

The estimated rate ratio of mepolizumab vs. dupilumab in Population 1, adjusting for all covariates listed above, is 0.45, with the 95% credible interval (CrI) ranging from 0.25 to 0.85. For comparison, the respective estimated rate ratio for mepolizumab vs. dupilumab obtained from the MAIC and using a Negative Binomial distribution was 0.85, with a 95% CrI ranging from 0.45 to 1.65. Of note, the 95% CrI in the ML-NMR analysis is substantially wider than the 95% confidence interval (CI) in the MAIC.

Figure 2 summarises the results of the analysis performed for Population 2 and shows the estimated relative treatment effects of all pairs of treatments and in each of the five studies included.

The estimated rate ratio of mepolizumab vs. dupilumab in Population 2, adjusting for all covariates listed above (except E-RS:COPD score), is 0.85, with the 95% CrI ranging from 0.45 to 1.65. For comparison, the respective estimated rate ratio for mepolizumab vs. dupilumab obtained from the MAIC and using a Negative Binomial distribution was 0.85, with a 95% CrI ranging from 0.45 to 1.65.

Figure 2: RRs of number of moderate or severe exacerbations estimated from ML-NMR for all pairs of treatments and in all studies – Population 2



Abbreviations: ML-NMR, multi-level network meta regression; RR, rate ratio.

In summary, results from the ML-NMR are similar to results obtained from the MAICs in both populations (with a higher degree of uncertainty around estimates in the ML-NMR fitted to Population 1), highlighting the robustness of our analyses and the consistency of estimated results across the different methods used.

A3. The company states that proportional hazards were used in the calculation of hazard ratios for ‘time to first exacerbation’ (CS Section 2.10.6.2, page 115). Could the company please provide evidence that the proportional hazard assumption was not violated (including Kaplan-Meier curves). If the assumption is violated could the company please conduct updated analyses that control for this violation (i.e., non-proportional hazards). If proportionality can be assumed, the company should also consider other modelling methods for sensitivity analyses (e.g., Weibull, Gompertz, and exponential methods) to show which is the most robust for the current scenario.

To assess whether the proportional hazard (PH) assumption can be assumed for the comparison between mepolizumab and placebo in the MAICs, we have created

Kaplan Meier (KM) curves, log-cumulative hazard plots and Schoenfeld residual plots for the treatment variable. In addition, a Schoenfeld test evaluating independence between Schoenfeld residuals for the treatment variable and time was performed, in which a p-value above 0.05 indicates a lack of association between residuals and time, thus supporting the PH assumption.

1. Defining chronic bronchitis on investigator assessment (using restricted population from the MATINEE trial)

Figure 3 shows the KM curve for time-to-first moderate/severe exacerbation by treatment arm (measured in days). The two curves are parallel, do not cross, and the gap between the curves is widening over time. This indicates that the PH assumption is met.

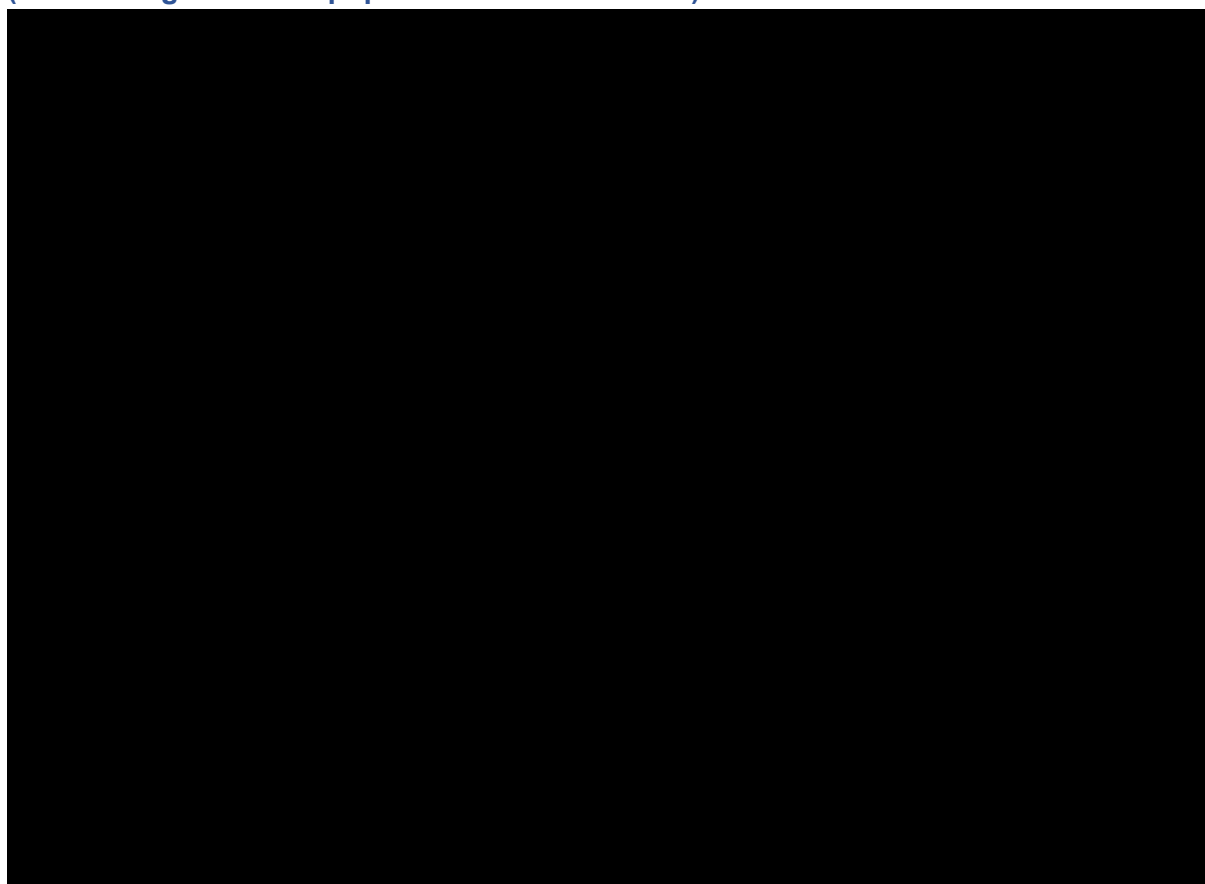
Figure 4 shows the log-cumulative hazard plot for time-to-first moderate/severe exacerbation by treatment arm. The plot shows approximately parallel curves, also indicating that the PH assumption is met.

Figure 5 shows the Schoenfeld residual plot for the treatment variable for time-to-first moderate/severe exacerbation. The plot shows points scattered randomly around zero, with no discernible trend. Together with a p-value of 0.35 for the Schoenfeld test, above 0.05, this also supports the PH assumption.

Based on the Cox PH model, a hazard ratio (HR) of [REDACTED] has been estimated for mepolizumab vs. placebo in the MAIC.

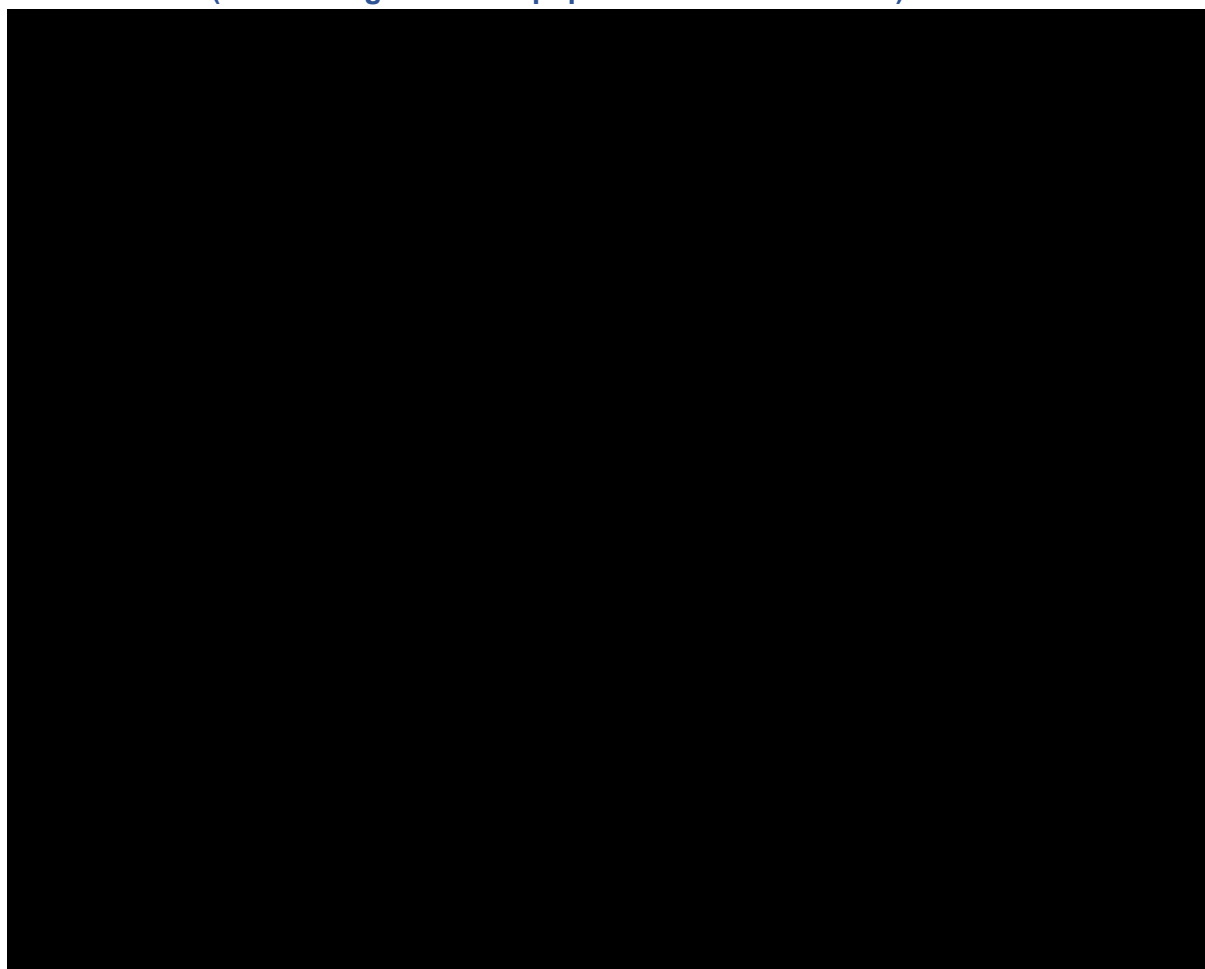
As a sensitivity analysis, we have now also estimated the HR using parametric PH models, namely the Exponential, Weibull, and Gompertz models. HRs from these parametric models are very similar to those from the Cox PH model: [REDACTED] for the Weibull model; [REDACTED] for the Exponential model; and [REDACTED] for the Gompertz model.

Figure 3: KM curve for time-to-first moderate/severe exacerbation by treatment arm (MAIC using restricted population from MATINEE)



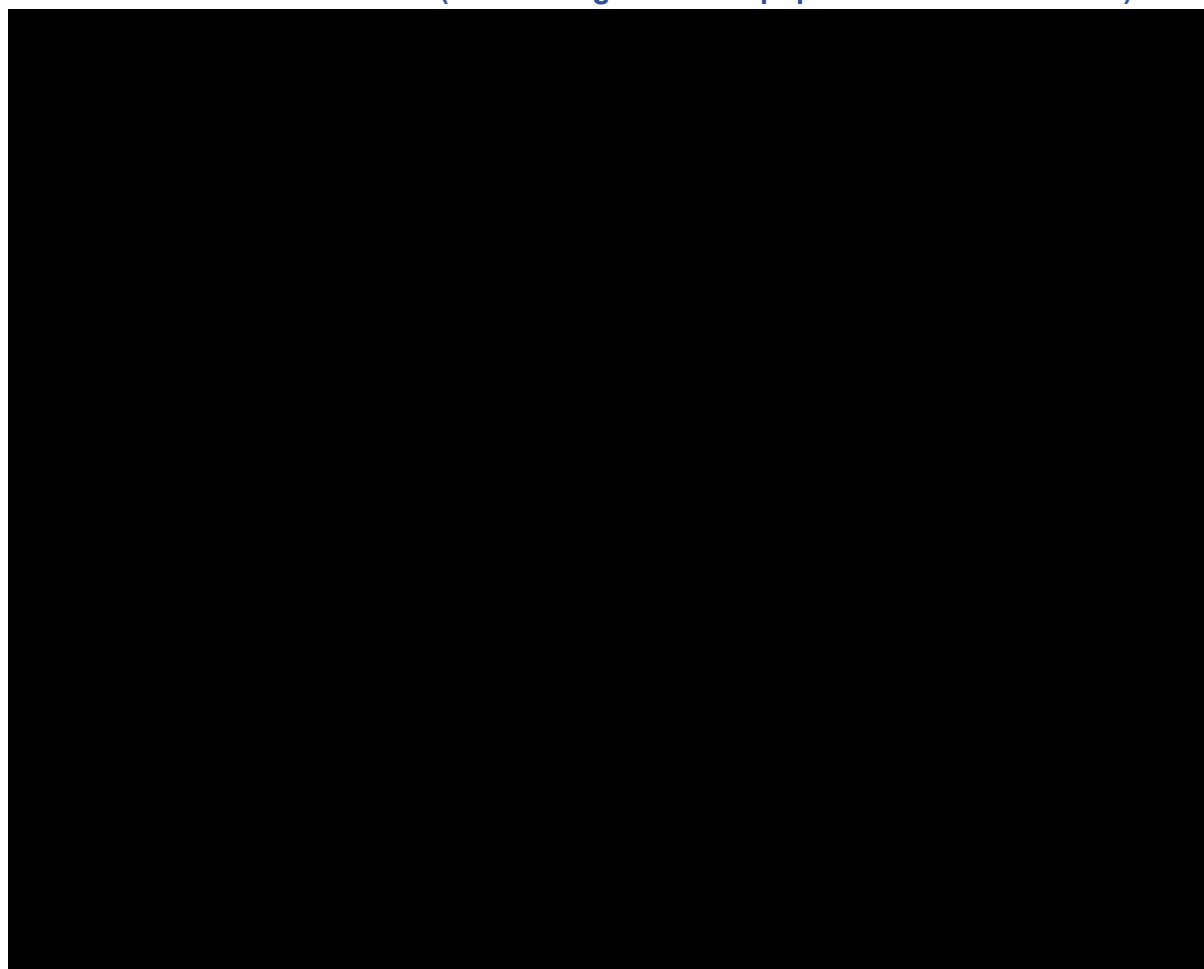
Abbreviations: KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison.

Figure 4: Log-cumulative hazard plot for time-to-first moderate/severe exacerbation by treatment arm (MAIC using restricted population from MATINEE)



Abbreviations: MAIC, matching-adjusted indirect comparison.

Figure 5: Schoenfeld residual plot for the treatment variable for time-to-first moderate/severe exacerbation (MAIC using restricted population from MATINEE)



Abbreviations: MAIC, matching-adjusted indirect comparison.

2. Defining chronic bronchitis based on SGRQ-C responses at baseline (using restricted population from the pooled MATINEE/METREX/METREO trials)

Figure 6 shows the KM curve for time-to-first moderate/severe exacerbation by treatment arm. The two curves are parallel, do not cross, and the gap between the curves is widening over time. Convergence towards the end of the KM curves is considered to be artefactual due to the small number of patients at risk. This indicates that the PH assumption is met.

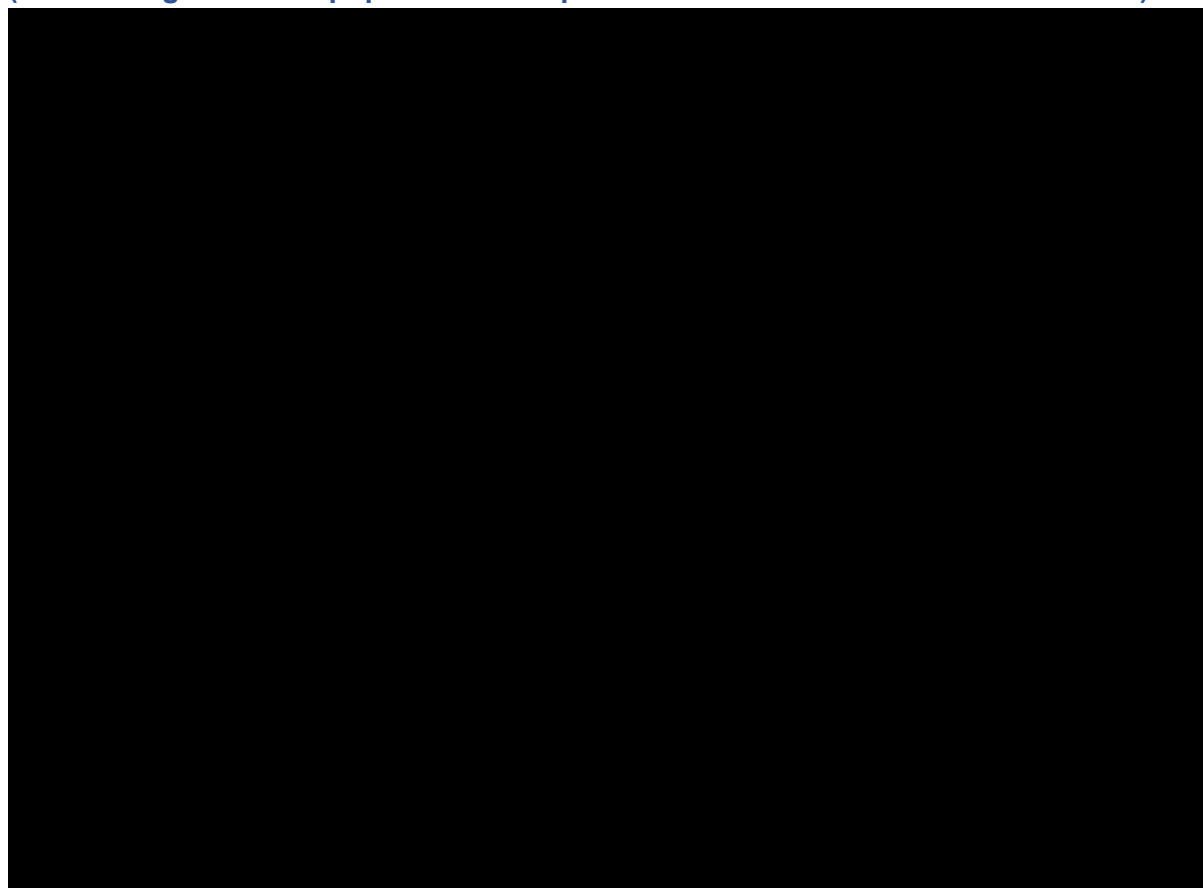
Figure 7 shows the log-cumulative hazard plot for time-to-first moderate/severe exacerbation by treatment arm. The plot shows parallel curves, which do not diverge or cross, also indicating that the PH assumption is met.

Figure 8 shows the Schoenfeld residual plot for the treatment variable for time-to-first moderate/severe exacerbation. The plot shows points scattered randomly around zero, with no discernible trend. Together with a p-value of 0.83 for the Schoenfeld test, above 0.05, this also supports the PH assumption.

Based on the Cox PH model, a HR of [REDACTED] has been estimated for mepolizumab vs. placebo in the MAIC.

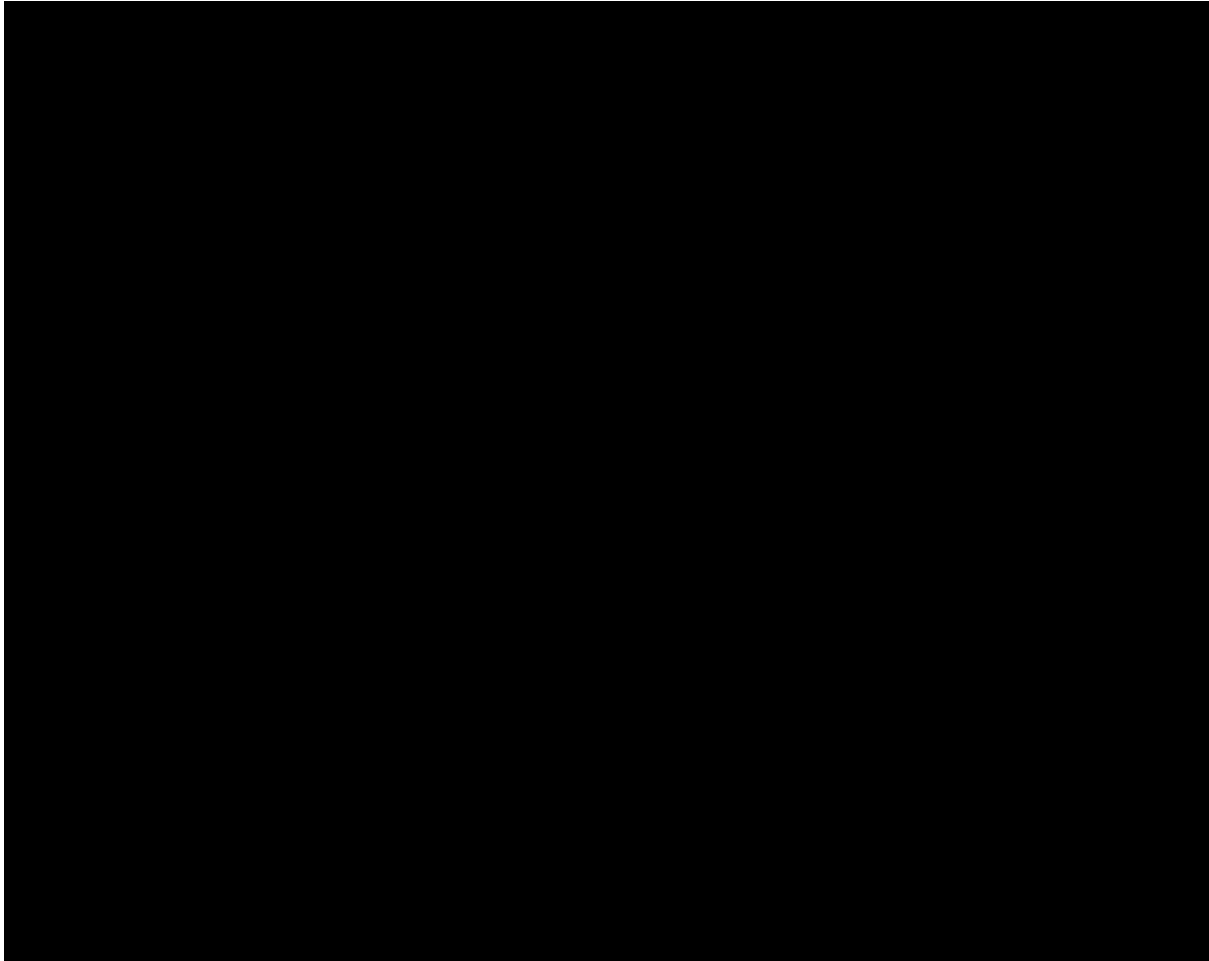
As a sensitivity analysis, we have now also estimated the HR using parametric PH models, namely the Exponential, Weibull and Gompertz models. HRs from these parametric models are very similar to those from the Cox PH model: [REDACTED] for the Weibull model; [REDACTED] for the Exponential model; and [REDACTED] for the Gompertz model.

Figure 6: KM curve for time-to-first moderate/severe exacerbation by treatment arm (MAIC using restricted population from pooled MATINEE/METREX/METREO trials)



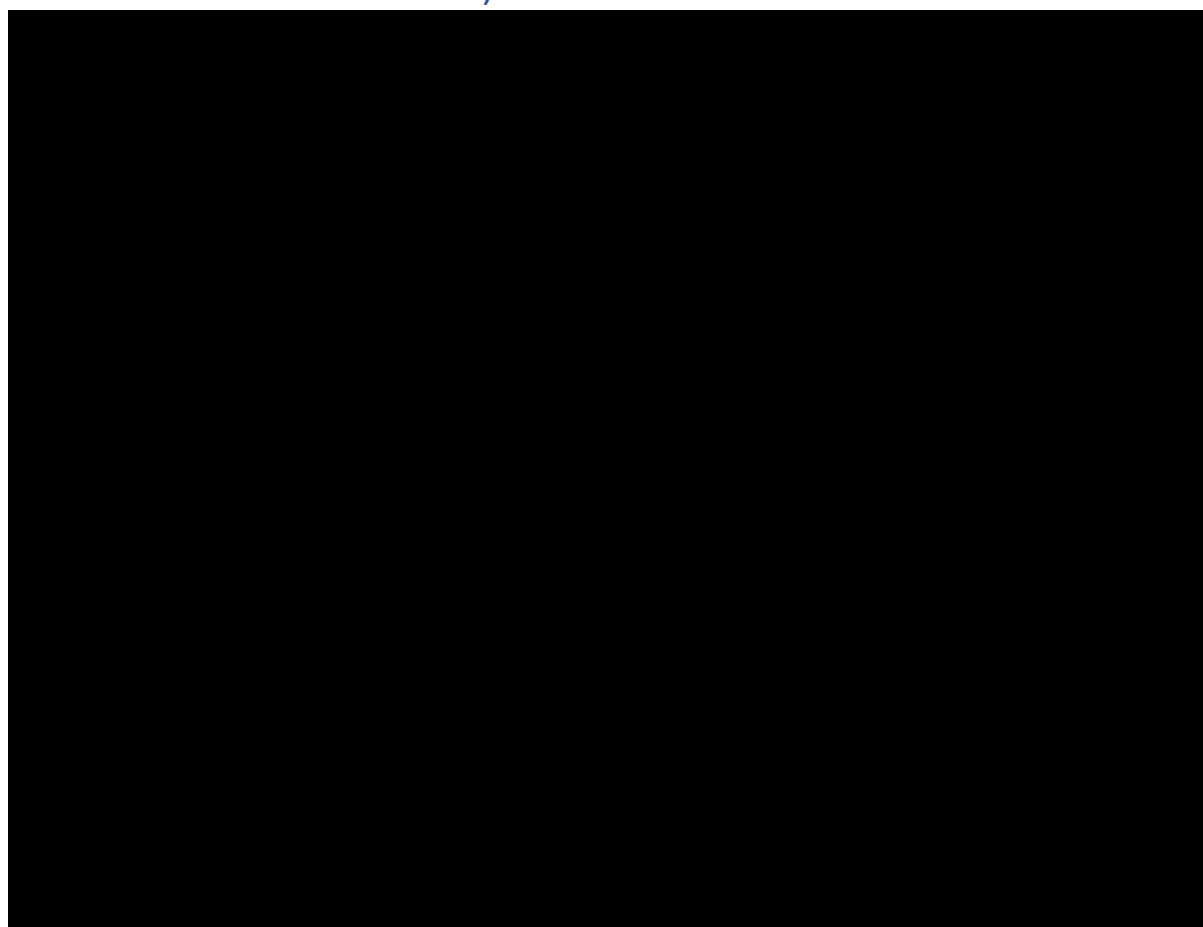
Abbreviations: KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; SC, subcutaneous.

Figure 7: Log-cumulative hazard plot for time-to-first moderate/severe exacerbation by treatment arm (MAIC using restricted population from pooled MATINEE/METREX/METREO trials)



Abbreviations: MAIC, matching-adjusted indirect comparison; SC, subcutaneous.

Figure 8: Schoenfeld residual plot for the treatment variable for time-to-first moderate/severe exacerbation (MAIC using restricted population from pooled MATINEE/METREX/METREO trials)



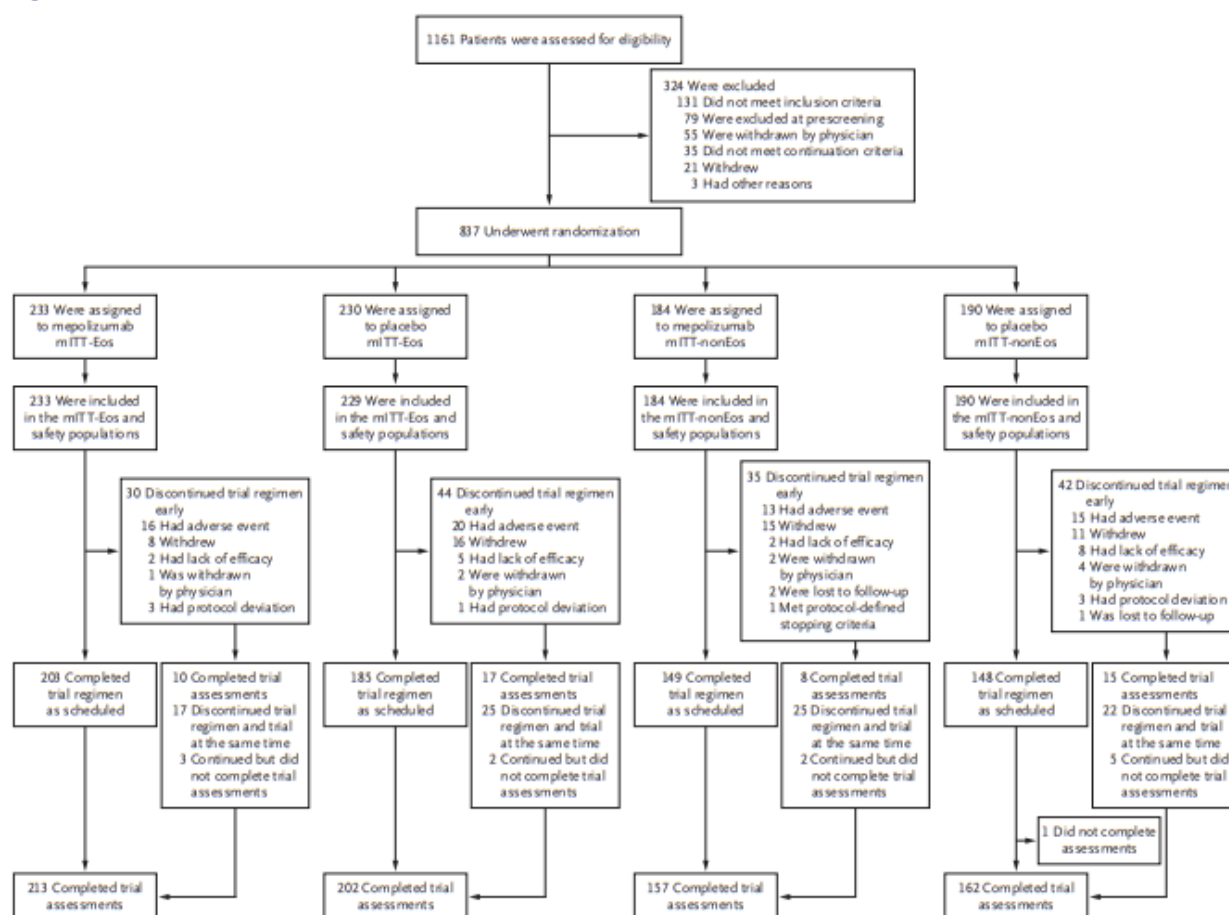
Abbreviations: MAIC, matching-adjusted indirect comparison

Clinical Trials

A4. Appendix B, Section B.2, pages 264-6. Please could the company provide participant flow diagrams for the METREX and METREO clinical trials in the same format as they have done for the MATINEE trial (including numbers assessed for eligibility, assigned to each group, withdrawals with reasons, and numbers of those who completed the study) in both the mepolizumab and placebo groups?

Participant disposition information for both the METREX and METREO trials is provided in Appendix J (Section J.2.2, Table 9), although in tabular rather than flow-diagram format. The participant flow diagrams for METREX and METREO are provided in Figure 9 and Figure 10, respectively.

Figure 9: Enrolment, randomisation, and follow-up in METREX

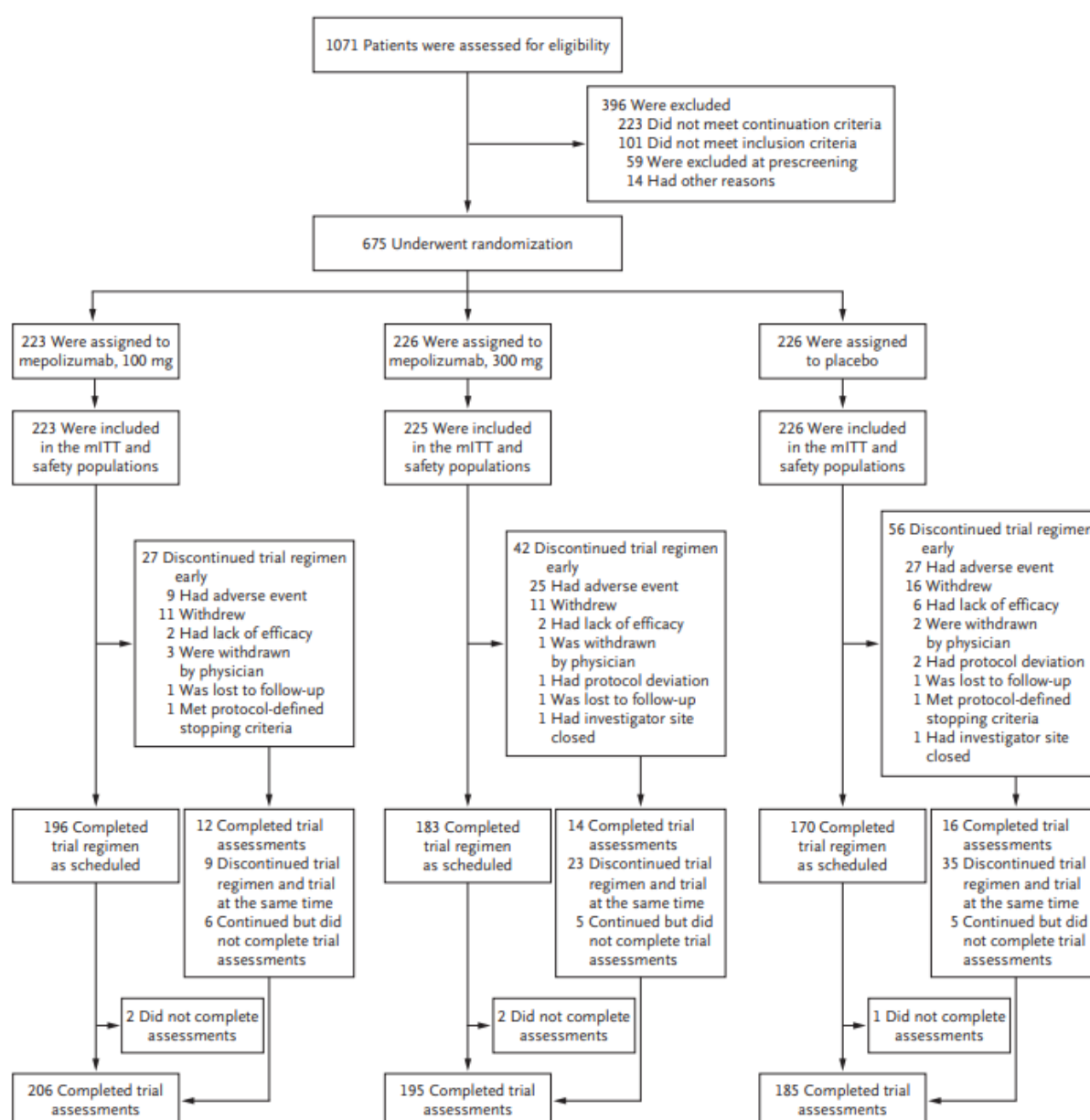


Source: Pavord 2017 (4).

The METREX overall modified intention-to-treat population included patients who received at least one dose of mepolizumab or placebo; within this population, the METREX mITT-EOS included patients with an eosinophil count of ≥ 150 per cubic millimetre at screening or at least 300 per cubic millimetre within the previous year, and the mITT population without an eosinophilic phenotype (mITT-nonEos) included all other patients.

Abbreviations: mITT-Eos, modified intention-to-treat population with an eosinophilic phenotype; mITT-nonEos, modified intention-to-treat population without an eosinophilic phenotype.

Figure 10: Enrolment, randomisation, and follow-up in METREO



Source: Pavord 2017 (4).

One patient who was excluded before randomization did not meet the inclusion criteria or the continuation criteria and is therefore included in both exclusion categories. The METREO mITT population included patients who received at least one dose of mepolizumab or placebo.

Abbreviations: mITT, modified intention-to-treat.

A5. CS Table 30 (page 104). In the MATINEE, METREX and METREO trials, quality-of-life was assessed at Week 52 (w52) using measures including the SGRQ-C. Please could the company provide results (baseline score, final scores and change from baseline scores) for SGRQ-C domain results (Symptoms, Activity, and Impact) separately for mild, moderate, severe and very severe COPD populations?

In the overall MATINEE population, the mean decrease in SGRQ total and domain scores from baseline to Week 52 was numerically higher with mepolizumab versus placebo (Table 1) (5). Across Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages, numerical improvements generally favoured mepolizumab, with the exception of some outcomes in GOLD 4. By Week 52, a ≥ 4 -point difference was observed in the total SGRQ score for mepolizumab compared with placebo in patients with GOLD 2. Additionally, ≥ 4 -point differences favouring mepolizumab were observed in the SGRQ Impacts domain for patients with GOLD 2 (-5.0) and GOLD 3 (-5.0) disease. A ≥ 4 -point difference was also observed in the SGRQ Activity domain for both GOLD 2 (-5.6) and GOLD 3 (-5.6). No ≥ 4 -point differences were observed in GOLD 4 (Table 1) (5).

Table 1: Mean change from baseline in SGRQ domain scores through Week 52 in the overall MATINEE population and mean change from baseline in SGRQ domain scores through Week 52 for GOLD subgroups

	Placebo	Mepo 100 mg
Overall population		
n	383	380
Total score	-5.7 (0.9)	-8.0 (0.9)
Difference (95% CI) (mepolizumab vs placebo)	-	-2.3 (-4.6, 0.1)
n	334	338
Activity	-4.9 (18.7)	-7.4 (19.9)
Difference (mepolizumab vs placebo)	-	-2.5
Symptoms	-9.0 (18.8)	-10.7 (19.5)
Difference (mepolizumab vs placebo)	-	-1.7
Impacts	-5.4 (20.9)	-9.4 (20.5)
Difference (mepolizumab vs placebo)	-	-4.0
GOLD 2		
n	174	161
Total score	-6.3 (1.2)	-10.3 (1.3)
Difference (95% CI) (mepolizumab vs placebo)	-	-4.0 (-7.6, -0.6)

	Placebo	Mepo 100 mg
n	181	168
Activity	-4.8 (18.4)	-10.4 (21.4)
Difference (mepolizumab vs placebo)	-	-5.6
Symptoms	-10.4 (18.0)	-12.7 (20.4)
Difference (mepolizumab vs placebo)	-	-2.3
Impacts	-5.7 (19.6)	-10.7 (20.1)
Difference (mepolizumab vs placebo)	-	-5.0
GOLD 3		
n	150	164
Total score	-5.6 (1.4)	-7.1 (1.4)
Difference (95% CI) (mepolizumab vs placebo)	-	-1.5 (-5.3, 2.4)
n	160	180
Activity	-4.7 (20.9)	-6.6 (19.9)
Difference (mepolizumab vs placebo)	-	-5.6
Symptoms	-10.4 (18.0)	-12.7 (20.4)
Difference (mepolizumab vs placebo)	-	-2.3
Impacts	-5.7 (19.6)	-10.7 (20.1)
Difference (mepolizumab vs placebo)	-	-5.0
GOLD 4		
n	56	53
Total score	-4.0 (1.8)	-3.1 (1.9)
Difference (95% CI) (mepolizumab vs placebo)	-	0.9 (-4.3, 6.1)
n	57	53
Activity	-5.6 (13.6)	0.0 (11.5)
Difference (mepolizumab vs placebo)	-	5.6
Symptoms	-4.8 (17.8)	-6.4 (18.5)
Difference (mepolizumab vs placebo)	-	-1.6
Impacts	-4.0 (19.3)	-4.5 (18.6)
Difference (mepolizumab vs placebo)	-	-0.5

Source: Jones *et al.*, 2025 (5)

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disorder; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mepo, mepolizumab; SGRQ-C, St. George's Respiratory Questionnaire COPD-specific version; vs, versus.

A6. Clinical advice to the EAG emphasised the critical role of smoking cessation and pulmonary rehabilitation in COPD management. Therefore, could the company please confirm:

- a. If receipt of pulmonary rehabilitation and/or smoking cessation was documented for patients enrolled in the MATINEE, METREX and METREO clinical trials where relevant? If so:**
- b. What proportion of these participants in the mepolizumab and placebo groups had access to these interventions in each clinical trial?**
- c. Can the company provide subgroup analyses showing the effectiveness of mepolizumab in attenders and non-attenders of pulmonary rehabilitation and/or smoking cessation interventions for relevant patients in the mepolizumab and placebo groups in each trial?**

Smoking cessation counselling was administered in the trials, but attendance was not recorded in the case report form (CRF). Similarly, participants were not allowed to enrol if they were in the active phase of pulmonary rehabilitation (participation in acute-phase pulmonary rehabilitation within 4 weeks prior to screening was an exclusion criterion); however, beyond that, a history of pulmonary rehabilitation or rehabilitation during the study was not recorded. It is therefore not possible to provide responses to questions A6b and A6c. Notably, only 28% of participants in the trial were current smokers; as such, any assessment of the impact of smoking cessation on outcomes during the trial would be based on a relatively small subgroup of participants.

A7. MATINEE clinical study report (6), Section 5.1.2.2.15 (page 148). The treatment effect of mepolizumab versus placebo was assessed by treatment duration (52 weeks versus up to 104 weeks). Mepolizumab was less effective on the rate of moderate/severe exacerbations in the subgroup enrolled for 52 weeks than on those enrolled for up to 104 weeks. Please could the company provide a table comparing the baseline characteristics of participants enrolled for 52 weeks with those enrolled for 104 weeks?

The relevant tables from the MATINEE clinical study report (CSR) containing the baseline characteristics are provided in Table 2. Baseline disease and demographic characteristics were generally similar between the 52 weeks fixed duration and 104 weeks variable duration subgroups.

Table 2: MATINEE: Participant baseline characteristics up to 52 weeks fixed duration and 104 weeks variable duration (mITT population)

Characteristic	Enrolled up to 52 weeks fixed duration		Enrolled up to 104 weeks variable duration	
	Placebo (N=175)	Mepo (N=170)	Placebo (N=226)	Mepo (N=233)
Age				
Mean (SD)				
Median (min, max)				
Age group years, n (%)				
<40				
40 to <65				
≥65 years				
Sex, n (%)				
Female				
Male				
Ethnicity, n (%)				
Hispanic or Latino				
Not Hispanic or Latino				
Race, n (%)				
American Indian/Alaskan Native				
Asian				
Black or African American				
Native Hawaiian or Other Pacific Islander				
White				
Mixed Race				
Height (cm) mean (SD)				
Weight (kg) mean (SD)				
BMI kg/m² mean (SD)				
Duration of COPD ≥10 years n (%)				
Mean duration of COPD (years [SD])				
Severity of airflow limitation[†], n (%)				
Mild ≥80% predicted				
Moderate: ≥50% <80% predicted				
Severe: ≥30% <50% predicted				
Very severe: <30%				
CV comorbidity[‡], n (%)				

Characteristic	Enrolled up to 52 weeks fixed duration		Enrolled up to 104 weeks variable duration	
	Placebo (N=175)	Mepo (N=170)	Placebo (N=226)	Mepo (N=233)
Other comorbidity [†] , n (%)	████	████	████	████
mMRC score at screening, n (%)				
mMRC <2	████	████	████	████
mMRC ≥2	████	████	████	████
Missing	████	████	████	████
Ever diagnosed with GERD, n (%)	████	████	████	████
Number of moderate/severe exacerbations, mean (SD)	████	████	████	████

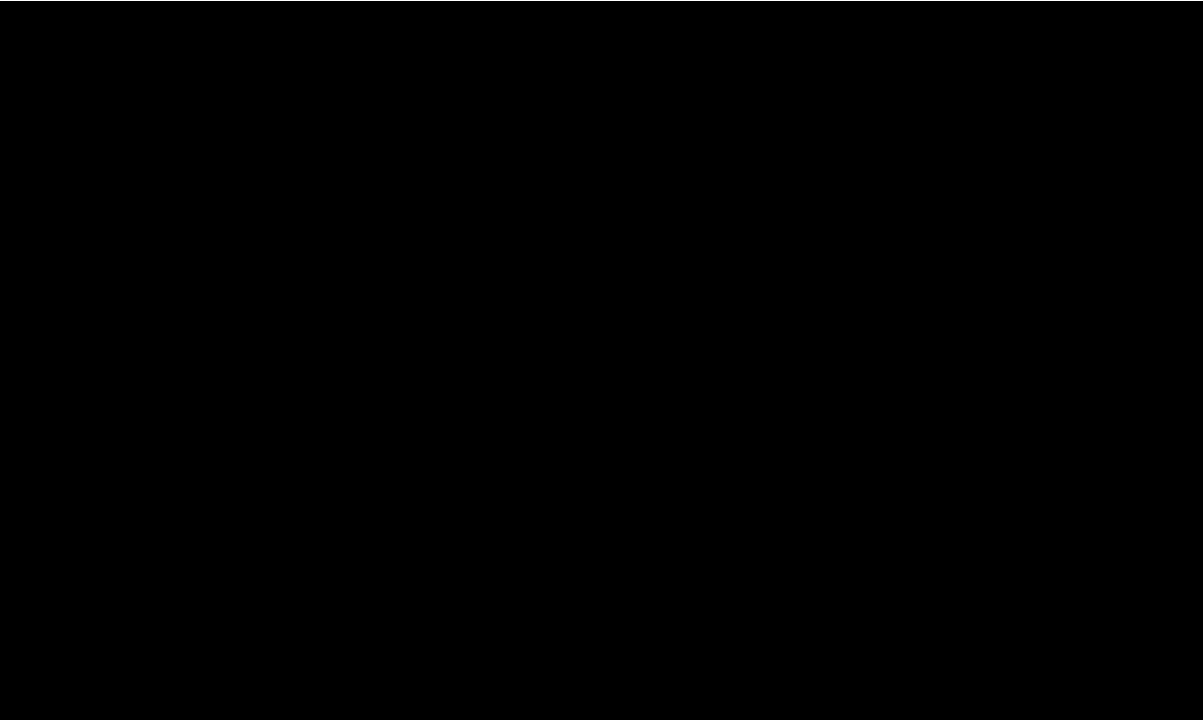
Source: Table 1.19, Table 1.20, Table 10 & Table 11 MATINEE CSR (6)

†Classification based on post-bronchodilator FEV₁ at Screening, GOLD Guidelines for COPD; ‡ CV disease comorbidity was defined as past/current medical conditions in the Cardiac Disorder category recorded on the medical conditions CRF (angina pectoris, coronary artery disease, myocardial infarction, arrhythmia, and congestive heart failure) or participants with a history/previous episode of heart failure on the CV Congestive Heart Failure CRF; ¶ Participants with Other comorbidity are defined as participants with any past or current medical condition other than under Cardiac Disorders.

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRF, case report form; CV, cardiovascular; FEV₁, forced expiratory volume in 1 second; GERD, gastroesophageal reflux disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mITT, modified intention-to-treat; mMRC, modified Medical Research Council; SD, standard deviation.

It is also important to note the 52 weeks fixed duration group in MATINEE was enrolled predominantly between 2019–2021, during the height of the COVID pandemic (Figure 11), with pandemic-related disruptions potentially impacting health-care delivery, background infection risk, and patient behaviour.

Figure 11: MATINEE: Participant enrolment over time (mITT)



Source: Figure 2 MATINEE CSR (6).
Abbreviations: mITT, modified intention-to-treat.

Post-hoc analyses suggest the difference in efficacy between the fixed and variable groups might reflect shifts in exacerbation patterns and other disruptions during the pandemic (Table 3).

Table 3: MATINEE: Rate of moderate/severe exacerbations by time periods related to COVID pandemic (mITT)

	Unadjusted annualised rate of exacerbations			Adjusted annualised rate of exacerbations		
	Placebo	Mepo	RR (95% CI)	Placebo	Mepo	RR (95% CI)
Start of study to date before start of COVID-19 pandemic						
–						
Months after start of COVID-19 pandemic						
>0–≤6						
>6–≤12						
>12–≤18						
>18–≤24						
>24–30						
>30–≤36						
>36–≤42						
<42–≤48						
>48						

Note: Start of the studyL 30 October 2019, end of study: 08 August 2024; Start of COVID-19 pandemic per WHO media briefing: 11 March 2020.
Abbreviations: CI, confidence interval; mepo, mepolizumab; mITT, modified intention-to-treat; RR, rate ratio; WHO, World Health Organization.

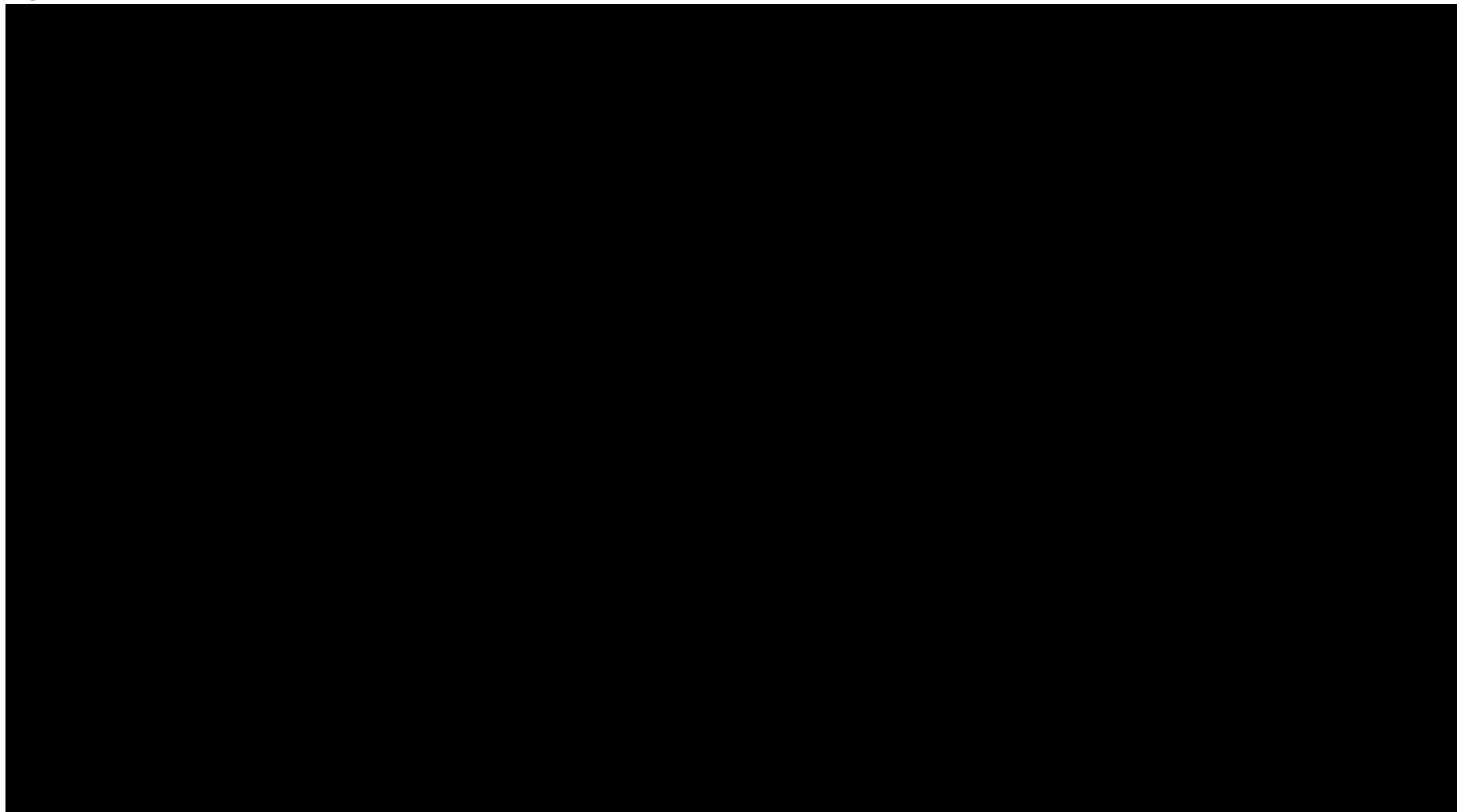
A8. The use of inhaled corticosteroids (ICS) is associated with adverse effects, therefore a potential benefit of mepolizumab could be a reduction in the use of these drugs. Could the company please confirm if the effect of mepolizumab treatment on ICS use/tapering was assessed in the MATINEE, METREX or METREO clinical trials? If so, please could the company provide this data?

The MATINEE (6), METREX (7), and METREO (8) clinical trials did not assess the effect of mepolizumab on maintenance inhaled corticosteroid (ICS) use or ICS tapering. In all three studies, background ICS therapy was considered part of standard-of-care (SoC) and was required to remain stable throughout the treatment period unless a change was clinically necessary (e.g., to treat an exacerbation).

Rescue medication use (including short-acting bronchodilators or short-term increases in ICS during exacerbations) was recorded as part of exacerbation management, but this does not constitute an assessment of ICS tapering or a formal measurement of ICS reduction as an outcome. As such, no analyses of ICS reduction, tapering, or sustained decreases in ICS dose were performed in MATINEE (6), METREX (7), and METREO (8), and therefore no data are available to report on this outcome.

The mean number of occasions of rescue medication use in the trials is provided in Figure 12. Analysis of the change from baseline in the mean number of occasions of rescue medication use is provided in Table 4.

Figure 12: Mean number of occasions of rescue medication use in (A) MATINEE (mITT) (B) METREX (mITT-H), and (C) METREO (mITT)



Source: Figure 33 MATINEE CSR (6); Figure 17 METREX CSR (7); Figure 21 METREO CSR (8).

Vertical bars represent 95% CIs.

Abbreviations: CI, confidence interval; mITT, modified intention-to-treat; mITT-H, modified intention-to-treat high stratum (included participants with a screening blood eosinophil count of ≥ 150 cells/ μ L or a historical blood eosinophil count of ≥ 300 cells/ μ L); SC, subcutaneous.

Table 4: Analysis of mean number of occasions of rescue medication use

Weeks 49–52	MATINEE‡	METREX¶		METREO¶			
	Placebo (N=401)	Mepo 100 mg (N=403)	Placebo (N=229)	Mepo 100 mg (N=233)	Placebo (N=226)	Mepo 100 mg (N=223)	Mepo 300 mg (N=225)
Population	mITT	mITT-H		mITT			
N with analysable data							
N with analysable data at time point							
LS mean (SE)							
LS mean change (SE)							
Difference (95% CI)							
p-value							

Source: Table 44 MATINEE CSR (6); Table 46 METREX CSR (7); Table 46 METREO CSR (8)

‡Analysis performed using MMRM with covariates of treatment group, geographic region, baseline, smoking status (current versus former smoker), visit plus interaction terms for visit by baseline and visit by treatment group. Estimates are based on weighting applied to each level of class variable determined from observed proportions; ¶Analysis performed using MMRM with covariates of baseline, geographic region, smoking status (current vs. never/ex-smoker), treatment, 4-week period plus interaction terms for 4-week period by baseline and 4-week period by treatment group. Estimates are based on weighting applied to each level of class variable determined from observed proportions

Abbreviations: CI, confidence interval; LS, least squares; mepo, mepolizumab; MMRM, mixed model repeated measured; mITT, modified intention-to-treat; mITT-H, modified intention-to-treat high stratum.

Section B: Clarification on cost-effectiveness data

B1. CS Section 3.3.5.2 (page 160). Could the company please clarify why only the standardised mortality ratio (SMR) value of 2.50 for severe COPD has been applied? The reference Samyshkin et al. (2014)(9) reports a SMR value of 3.85 for very severe COPD. We understand the company has conducted a scenario analysis in which the SMR for COPD was not included in the model, however the tornado diagrams in Figure 14 (page 185) and Figure 15 (page 186) show that SMR is among the top 10 drivers of incremental cost-effectiveness ratio (ICER). Applying a SMR=3.85 may therefore impact the currently reported ICER and be of interest to committee. Could the company please provide an additional scenario analysis using this SMR?

The pooled mITT-300 trial population with very severe COPD was 12.8%, whereas 40.4% had severe COPD, and 46.7% had moderate COPD.

A value of 2.5 was aligned with the source used in the roflumilast NICE submission (10) and is similar to the standardised mortality ratio (SMR) reported for patients with severe COPD (2.33) in Whittaker *et al.*, 2024 (11), which estimated all-cause mortality HRs associated with COPD severity based on an English dataset and was used to inform the company base case in the dupilumab appraisal (12). Two alternative sources (Leivseth *et al.*, 2013 (13), and Shavelle *et al.*, 2009 (14)) show similar or lower SMR values for severe COPD compared with Whittaker *et al.*, 2024:

- 1.77 for severe (forced expiratory volume in 1 second (FEV₁) 30 to 49% of predicted) from Leivseth *et al.*, (13)
- 1.4 for COPD stage 2 and 2.6 for COPD Stage 3 or 4 from Shavelle *et al.*, 2009 (14).

The use of a severe COPD SMR of 2.5 could be considered conservative, particularly when factoring in that 46.7% of the pooled modified intention-to-treat (mITT)-300 trial population were classified as having moderate COPD.

As such, applying an SMR of 3.85 would likely significantly overestimate the SMR for the population as a whole, given that 12.8% of patients in the mITT-300 trial population had very severe COPD. The value used of 2.5 is also considered to be aligned with other sources identified. When tested within one-way sensitivity analysis (OWSA) and comparing with SoC, it was not found to be within the top 10 drivers.

Nevertheless, it is recognised that adjustment of the SMR is a relevant scenario, and a scenario has been undertaken using an SMR of 3.85. Results are presented in Table 16 of Appendix A, where a small impact on the incremental cost-effectiveness ratio (ICER) is observed.

B2. CS Section 3.3.5.3 (page 160-161)

- a. Could the company clarify why they preferred to use the case-fatality rates (CFR) from Hoogendoorn et al. (2011)?(15) This paper was a meta-analysis of six studies, none of which were based in the UK, with the most recent study in the meta-analysis using data from 2005.**

Case-fatality rates (CFR) were applied in the model to represent the increased risk of mortality associated with severe exacerbations. Use of a CFR aligns with the

Company and external assessment group (EAG) preferred approach at Appraisal Committee Meeting 2 (ACM2) in the dupilumab NICE submission (12) and the committee preferred approach in the roflumilast NICE submission (10).

The CFRs from Hoogendoorn *et al.*, 2011 (15) were used because this analysis focused specifically on estimating mortality following COPD exacerbations, rather than overall COPD-related mortality. Hoogendoorn *et al.*, (15) conducted a large meta-analysis including almost 60,000 people from across six studies and reporting survival rates for at least 1.5 years post-exacerbation. The study focused specifically on exacerbations and aimed to estimate the case fatality of a severe COPD exacerbation including the time period after hospitalisation. By isolating mortality attributable to severe exacerbations, including deaths occurring after hospital discharge, the study reduces potential confounding from general COPD mortality. Although none of the included studies included data from the United Kingdom (UK), with the most recent data from 2005, Hoogendoorn *et al.*, 2011 remains one of the few sources providing exacerbation-specific case-fatality estimates over an extended follow-up period. These exacerbation-focused CFRs were therefore considered the most appropriate available inputs for capturing mortality directly related to severe exacerbations in the model.

When focusing specifically on UK data, the 2023 National Asthma and COPD Audit Programme (NACAP), which uses data from 2018–20, found that 11.9% of patients with COPD died within 90 days after hospitalisation (16). This was used by EAG at ACM2 of the dupilumab appraisal, and at the time was the latest available data. A more recent audit value was used within a scenario in this submission, using the latest UK data from the National Respiratory Audit Programme (NRAP), based on data between 2021–23, and found a value of 14.2% of mortality within 90 days after hospitalisation.

The use of the CFR of 15.6% in the model is broadly in line with the latest UK based estimates. Using lower values from either of the NACAP or NRAP audits results in an ICER below £20,000 vs SoC.

- b. Samyshkin et al. (2014),(9) which was used as a source of SMR, also reports the age-adjusted CFR for range of age groups (64-85 years) and**

appears to draw on UK data. Could the company explain why the age-dependent CFR data from this study were not used?

Whilst Samyshkin *et al.*, 2014 (9) report use of UK data in their analysis, this data is from a 2008 UK National COPD Audit Report. The age adjustments are also based on using the ratio of age-specific risk of death in the general population to the risk of death at the age of 73 (the average age in the COPD audit report) to adjust the CFR value of 7.7% from the audit report, and therefore age-based CFR values are calculated rather than being based on raw age-related data.

It is important to highlight that an age-adjustment is also included within the company model, and is modelled from the multivariate analyses undertaken in Hoogendoorn *et al.*, (15) on the patient-level data, using a 1.041 relative risk for each unit increase in age (years), using the reference age from Hoogendoorn *et al.*, of 69. Therefore, adjusting the CFR for the age of the population within the model is included.

The CFR value of 14.2% used in a scenario within the company submission is from more recent UK NRAP audit data (17), as discussed in B2a, and is also age-adjusted as previously mentioned, although it should be noted that the mean age from the audit data is not reported, and therefore the mean age used for the age-adjustment is assumed to be the same as from Hoogendoorn *et al.*, *i.e.* age 69.

- c. The company states that the CFR has been tested in a scenario analysis using the 14.2% value reported in the National Respiratory Audit Programme (NRAP) clinical outcomes (2021-23) and outliers summary report from Royal College of Physicians.(17) Could the company provide a scenario analysis where age dependent CFRs based on Samyshkin *et al.* (2014),(9) are used, given they present the odds of having a higher CFR with increasing age?**

As mentioned in the response to B2b, the data for the CFR value of 14.2% in the scenario is based on more recent UK audit data than the data used within Samyshkin *et al.* 2014 (9). In addition, the age-adjustments to the CFR have been included in the model and are based on the multivariate analyses undertaken in Hoogendoorn *et al.*, on the patient-level data, looking at the relationship between mortality after an exacerbation resulting in hospitalisation, and age.

However, a scenario has been undertaken using the CFR value of 14.2% based on the NRAP 2021–23 data (considered more recent than the UK audit data used within Samyshkin *et al.* 2014), and age-adjusting this using the method within Samyshkin *et al.* 2014. The age-adjustment involves applying to the CFR; the ratio of age-specific risk of death in the general population to the risk of death at the age of 69 (the mean age from the NRAP report is not reported, therefore the mean age of 69 from Hoogendoorn *et al.* is assumed). This adjustment is made using the 2018–20 life tables incorporated within the economic model, and is also based on the general population mortality with the COPD SMR applied. Please see Table 16 in Appendix A for the results; this scenario has a small impact on the ICER.

B3. CS Section 3.3.4 (page 158). Could the company confirm that the 9.3% discontinuation probability in the first year for dupilumab has been adjusted for any COVID-19 related discontinuations? If not, could the company provide a scenario analysis using the adjusted discontinuation probability for dupilumab (including the justification and rationale for the adjustment or lack thereof)?

The 9.3% discontinuation probability in the first year for dupilumab was assumed in line with the probability reported in the dupilumab committee papers and includes COVID-19-related discontinuations (12). Removing COVID-related discontinuations results in a discontinuation rate of 8.5%.

As reported in the responses to EAG clarification questions in the dupilumab submission, the observed discontinuations in the pooled analysis due to non-COVID-related infections were very low compared with infections in the comparable pre-pandemic ETHOS study. Clinical experts to the company in the dupilumab NICE submission noted that whilst COVID infections increased during the trial period, there was a decrease in non-COVID-related infections. Given that the overall impact of the pandemic on all infections in the trial is unknown, and that COVID infection persists in the real-world now, the 9.3% discontinuation rate is considered more appropriate to use in the model.

Nevertheless, a scenario using 8.5% has been undertaken, and is reported in Table 16 in Appendix A. Dupilumab remains dominated compared with mepolizumab.

B4. CS Section 3.3.4 (page 158). The CS reports that only MATINEE trial data had a follow-up beyond 12 months and therefore was used for mepolizumab discontinuations in year 2 onwards (█████%). Could the company provide a scenario analysis in which the pooled mepolizumab discontinuation data for 10-12 months (█████%) are applied for 2 years and beyond until the lifetime horizon?

The data from beyond 1 year from MATINEE is considered more appropriate, because this uses discontinuation data for responders, which aligns with the methodology of the model whereby the incorporation of a stopping rule means that only patients who are considered responders to treatment remain on mepolizumab from Year 2 onwards. The application of discontinuation rates from a population which includes non-responders would therefore not be aligned with the responder population and would likely overestimate the discontinuation rate in responder patients.

For completeness, a scenario is included in Appendix A, which applies a discontinuation probability of █████% per cycle beyond 1 year, to both mepolizumab and dupilumab. This had a negligible impact on the results.

Alternative scenarios on the post 1-year discontinuation rates were also undertaken within the company submission, including

- Using the 15% annual discontinuation rate used in the dupilumab NICE Company submission based on real-world evidence (RWE) from an asthma study and clinical expert opinion to the Company (12, 18-20). This is used for mepolizumab and dupilumab in scenario analysis and translates to a per cycle probability of discontinuation of 3.68%.
- Using the █████% per cycle from MATINEE for mepolizumab, and 15% annual discontinuation rate from the dupilumab submission for dupilumab.

B5. CS Section 3.3.4 (page 158). The company reports using pooled estimates of discontinuation data, however, could the company clarify if they considered extrapolating the trial data using parametric fitting on the proportions discontinuing mepolizumab, and why it was not considered an appropriate approach for

discontinuation? Could the company please provide standard parametric curve fits for the trial data?

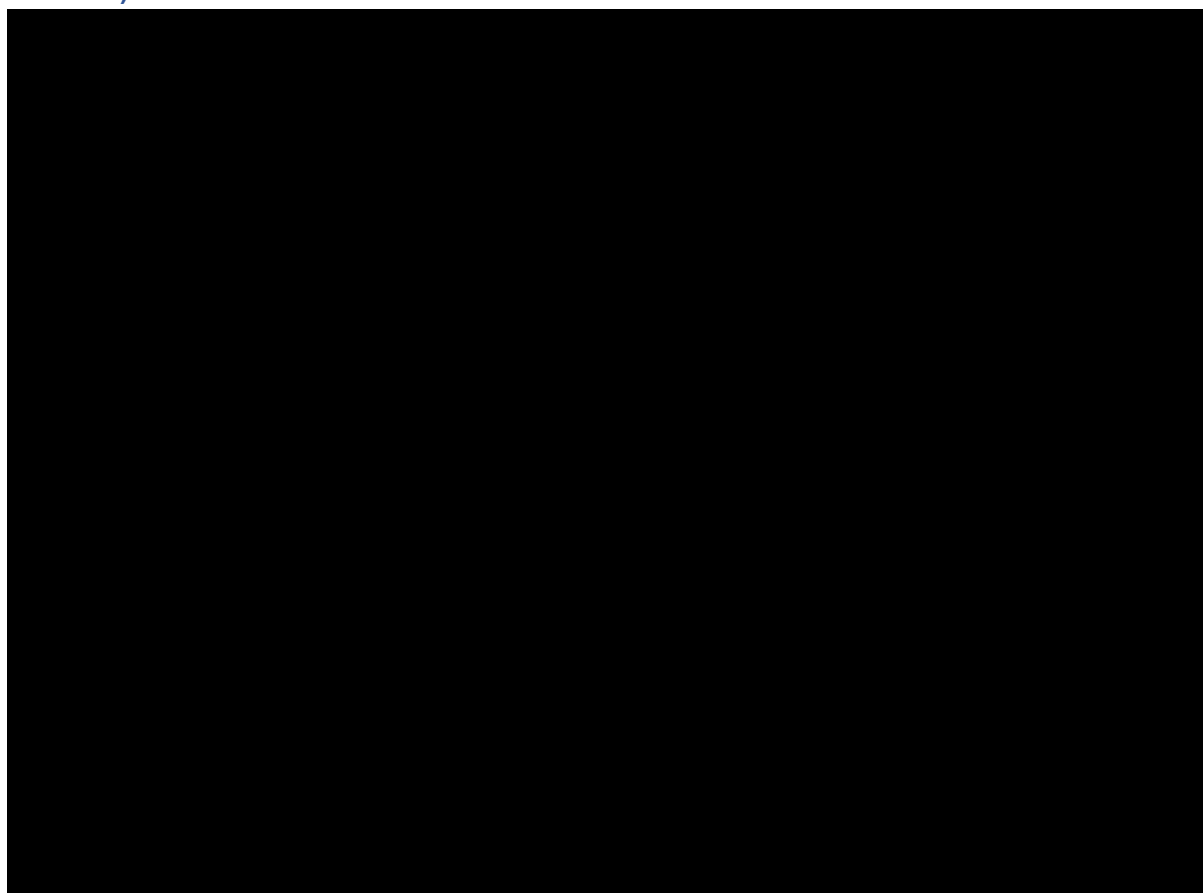
Beyond 1 year, only MATINEE included follow-up beyond 12 months. Therefore, the annualised discontinuation rate observed over the second year of the MATINEE trial for responders was converted to a probability of discontinuation per cycle and used in the model from Year 2 onwards for mepolizumab. The discontinuation rate was also adjusted for patient years of follow-up in the trial, as total follow-up fluctuated between patients.

Parametric curve fits for discontinuation beyond 52 weeks can be seen below. The following assumptions were made:

- Time was anchored at the 52-week visit, which typically falls close to, but not exactly at, Day 365.
- 'Responders' were defined as those meeting the stopping rule definition used within the economic model.
- The maximum follow-up in the observed data was 348 days.
- Time is reported in days.

The KM curve of observed data for the time-to-discontinuation with mepolizumab from Week 52 is provided in Figure 13.

Figure 13: KM-curve observed data (time-to discontinuation with mepolizumab, from week 52)



Abbreviations: KM, Kaplan-Meier.

Table 5 presents the goodness-of-fit statistics for the alternative parametric survival distributions, and the observed KM survival data alongside extrapolated survival curves based on fitted parametric models is provided in Figure 14. A summary of parameter estimates by distribution is provided in Appendix B.

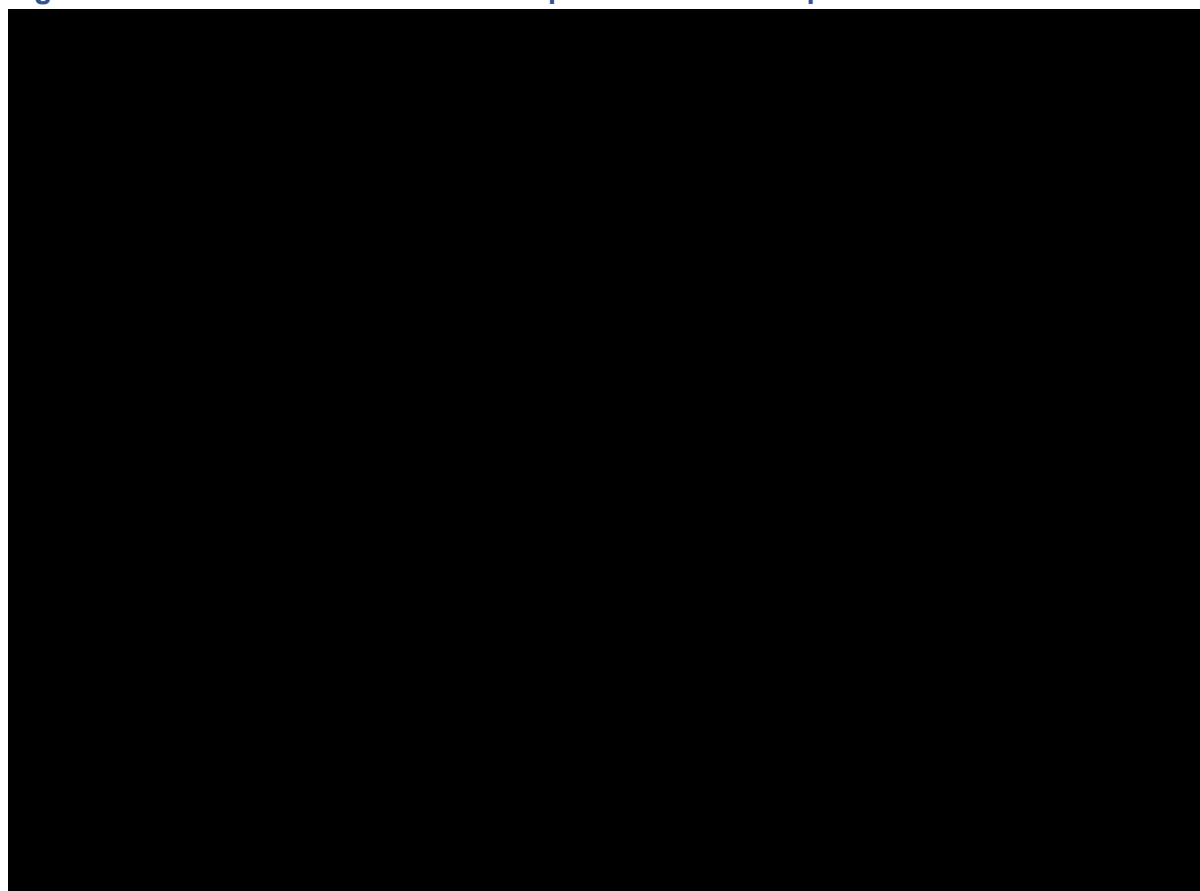
All models have a very similar fit within the observed part of the data, however Figure 14 shows that there is large variation in the discontinuation predicted over the longer term between the different distributions, highlighting the large amount of uncertainty from extrapolating the discontinuation data beyond 52 weeks. Therefore, extrapolation of the discontinuation data was not considered to be appropriate.

Table 5: Summary – model fit by distribution

distribution	AIC	BIC
exponential		
gamma		
gompertz		
llogistic		
lnormal		
weibull		

Abbreviations: AIC, Akaike Information Criterion; AICC, Corrected Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure 14: KM observed data and extrapolation based on parametric models

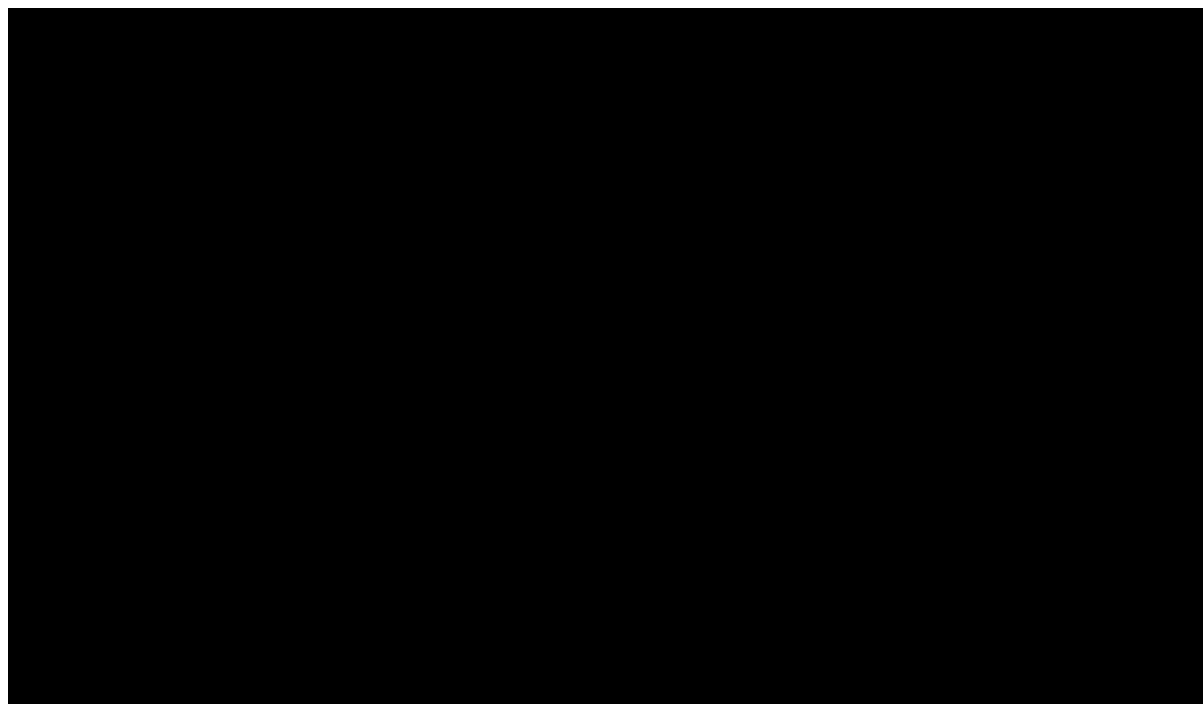


Abbreviations: KM, Kaplan-Meier.

As a comparison, Figure 15 shows discontinuation over time when using a constant per cycle discontinuation probability (model base-case of 1.54%) from 52 weeks (note this is assuming 52 weeks is time zero, following the method used above for deriving the parametric curves). The exponential parametric curve would be the closest approximation to the current approach, as this naturally assumes a constant hazard, with all other curves modelling a more rapid treatment discontinuation.

It is also important to note that testing alternative discontinuation values within the company submission had little impact on the cost-effectiveness (Figure 15 also showing the proportion remaining on treatment using this scenario), therefore discontinuation is not considered to be a big model driver.

Figure 15: Proportion remaining on mepolizumab treatment using constant per cycle discontinuation rate



B6. CS Section 3.5.2.1, Table 65.

- a. Could the company provide the calculation of the unit cost of an outpatient visit and confirm whether the value of £204.98 is correct? The EAG's calculation of the weighted average of Respiratory services, Outpatient attendances (codes 340 and 341) appear to be approximately £190. Please see table below:

Outpatient attendances	Weighted costs	Total Frequency
(codes 340)	389,466,942	1,932,732
(codes 341)	47,993,777	375,734
Total	437,460,719	2,308,466
Unit costs	$(437,460,719 / 2,308,466) = 189.50$	

The outpatient cost was derived from weighting the consultant-led costs for outpatient attendances, of codes 340 and 341. Please see Table 6 below for a summary of the calculation.

Table 6: Outpatient visit calculation

Outpatient attendances	Activity	Unit cost	Product
Code 340 – Consultant Led	1,375,631	211.82	£291,387,023
Code 341 – Consultant Led	209,229	160.01	£33,477,775
Unit costs	$(291,387,023 + 33,477,775) / (1,375,631 + 209,229) = 204.98$		

A scenario has been undertaken using the EAG's weighted outpatient cost, and results can be seen in Table 16 in Appendix A, with the outpatient cost having a negligible impact on results.

b. Oral corticosteroids (OCS), influenza vaccine use in COPD management and antibiotics use in moderate exacerbation management were sourced from GlobalData 2025. Could the company please provide access for EAG to verify these?

The costs of oral corticosteroids (OCS), influenza vaccine, and antibiotics, were correct at the time of sourcing, however costs change over time, particularly as the drugs are generic. The costs as of 25/11/25 are provided below.

The OCS price has since increased to £0.80 per pack for prednisolone 5 mg:

Drug Geography / Region	Brand Name	Company (Parent)	Generic Name	Dosage Form	Strength	Number of Units	Volume	Drug Type	Price Date	Ex-manufacturer Price (LCU)	Wholesale Price (LCU)
United Kingdom National	PREDNISOLONE	Crescent Pharma	PREDNISOLONE	TABLET	5 MG	28		Generic	28 Oct 2025	GBP 0.80 →	GBP 0.80 →

For antibiotics price, a lower cost generic has been identified at the current time for Amoxicillin 250 mg capsules of £0.70 per pack:

Drug Geography / Region	Brand Name	Company (Parent)	Generic Name	Dosage Form	Strength	Number of Units	Volume	Drug Type	Price Date	Ex-manufacturer Price (LCU)	Wholesale Price (LCU)
United Kingdom National	AMOXICILLIN RX FARMA	Rx Farma	AMOXICILLIN	CAPSULE	250 MG	21		Generic	28 Oct 2025	GBP 0.70 →	GBP 0.70 →

The influenza vaccine used for costing at the time the data was sourced, is no longer available in the market; an alternative can be found below at £17.55.

Clarification questions

	Drug Geography / Region	Brand Name	Company (Parent)	Generic Name	Dosage Form	Strength Comment	Number of Units	Volume	Drug Type	Price Date	Ex-manufacturer Price (LCU)	Wholesale Price (LCU)
2	United Kingdom National	ADJUVANTED TRIVALENT INFLUENZA VACCINE	Csl Group	INFLUENZA, INACTIVATED, +	SUSPENSION FOR +		1	0.5 ML	Branded	28 Oct 2025	GBP 17.55 →	GBP 17.55 →

It is important to reiterate that GlobalData POLI uses prices of drugs from the UK's Dictionary of Medicines and Devices, which is the same source used by the British National Formulary (BNF). All prices above have been checked with the BNF and correspond.

A summary of the costs used within the model, and those sourced above can be found below.

Table 7: Global data costs at the time of submission and at the current time of sourcing

Input	Product	Cost in submitted model	Cost from latest Globaldata
OCS	Prednisolone 5mg, 28 tablets per pack	£0.49	£0.80
Antibiotic	Amoxicillin 250mg, 21 capsules per pack	£5.00	£0.70
Influenza vaccine	Adjuvanted trivalent influenza vaccine, 0.5ml*	£13.50	£17.55

*The product previously costed of adjuvanted quadrivalent influenza vaccine is no longer available in the market

A scenario using these updated costs has been undertaken for completeness, and this has very little impact on the results (Table 16, Appendix A).

c. Could the company justify why the OCS use frequency in moderate exacerbation management ‘0.00’?

In Table 66 of the company submission, there is a reporting error within the table, whereby:

- The frequency per event for the OCS prescription should be 1.00, and
- The frequency per event for antibiotics should be 2.00.

A corrected version of the table is presented below in Table 8. Please note that the values were correct within the economic model itself.

Table 8: Moderate exacerbation resource use costs (correction to table 66 of company submission)

Resources	Cost per unit (£)	Frequency per event	Source for cost
A&E visit without admission	123.75	0.30	NHS reference costs 2023/24 (21) – Emergency Medicine, weighted average of Emergency Medicine, No investigation with No Significant Treatment (VB11Z)
Respiratory team visit	289.00	0.10	Episode assumed to comprise six 40-minute visits from either a band 6 (75%) or band 7 (25%) PSSRU 2023/24 (22)
GP Visit	45.00	1.00	Unit cost for a GP, Cost per surgery consultation lasting 10 mins (including qualifications and direct care staff costs) – unit costs of health and social care (22)
OCS (number of prescriptions)	0.49	1.00	GlobalData 2025 (23)
Antibiotics (number of prescriptions)	5.00	2.00	GlobalData 2025 (23)
Total costs per model cycle (£)	121.52		

Abbreviations: A&E, accident and emergency; GP, general practitioner; NHS, national health service; OCS, oral corticosteroids; PSSRU, personal social services research unit.

B7. CS Section 3.5.4.1. Table 68. The retirement age used in the company model is 66 years, and the EAG understands that the percentage early retirement after age 66 may not be reasonable. Moreover, the costs of productivity loss and costs of early retirement in the company CEA model, sheet “Costs”, cells V14-21 and W14-21 appear to have already taken the retirement percentage into account. However, in the company CEA model, there are built-in retirement percentages in all three trace sheets (Soc, Mepo, Dupi), in column H, which appear unreasonable for a Markov model. It also appears that the formula used

to calculate the indirect costs in column DM of sheets “Trace mepo” and “Trace dupi” is missing brackets and is incorrectly calculated.

a. Could the company clarify their approach to incorporating the early retirement percentage used in all three trace sheets?

Within the ‘costs’ sheet, in V14:V21, the costs being calculated are the indirect costs related to the productivity lost from exacerbations. The productivity loss is only applicable for patients who are below the age of retirement and employed (early retirees are excluded from the calculation). This formula takes into account (asterisk denotes multiplication):

- The proportion of the population employed under the retirement age of 66 *
- The average cost per working day (based on the number of working days per year and the average annual salary) *
- The number of days lost from exacerbations (varying by exacerbation type) *
- 1 minus the proportion retiring early (as no retirement loss is expected to occur as a result of exacerbation events).

For the calculations in W14:W21, on the indirect costs related early retirement, this takes into account (asterisk denotes multiplication):

- The excess retirement rate due to COPD (the proportion of patients retiring early due to COPD was estimated in Wacker *et al.*, 2016 (24) stratified by GOLD severity stage. These proportions are weighted by the proportion of patients in each GOLD severity category from the pooled trial analysis, resulting in 33% of patients with COPD retiring early, and then subtracted from this is the early retirement proportion of the general population) *
- The average cost per working day *
- The number of working days per cycle.

Column H on the model engines is representing the proportion of patients below the age of retirement (using a normal distribution centred around the retirement age), and these are multiplied with health state occupancy per state and the indirect costs per state to determine overall indirect costs.

This is also in line with the approach, and sources of data, previously used within the dupilumab appraisal.

- b. Could the company please check and confirm the indirect cost calculations in Column DM of sheets “Trace mepo” and “Trace dupi” are correct? If the current formula is incorrect, please provide an updated model and analysis where necessary.**

The calculations have been checked and are confirmed to be correct.

The formula does appear different for the SoC trace; however, this is a shorter formula than the other traces because there is no ‘health state occupancy – event distribution’ columns for discontinuation on the SoC trace, therefore the formulas are not meant to be identical between engines. This has been checked using the formula from the ‘Trace mepo’ sheet from column DM and applying it onto the ‘Trace SoC’ sheet in column CN, and the same results were derived as using the original formula on the SoC trace.

B8. Company submitted CEA model, Worksheet “Mortality”, F49 (and below). Could the company please clarify the rationale for the yellow highlighted formula used and whether it is correct? It is not clear why the formula cannot be written as shown in the highlighted green version.

`IF(IF(F$46=$I$46,$L$24*$L$32^($B49-L$33),IF(F$46=$M$46,$L$25*$L$32^($B49-$L$33),1-EXP(-INDEX('Life tables'!$S$15:$S$115,MATCH(Mortality!$B49,'Life tables'!$B$15:$B$115,0))))>1,1,(IF(F$46=$I$46,$L$24*$L$32^($B49-$L$33),IF(F$46=$M$46,$L$25*$L$32^($B49-$L$33),1-EXP(-INDEX('Life tables'!$S$15:$S$115,MATCH(Mortality!$B49,'Life tables'!$B$15:$B$115,0))))))`

`IF(1-EXP(-INDEX('Life tables'!$S$15:$S$115,MATCH(Mortality!$B49,'Life tables'!$B$15:$B$115,0)))>1,1,1-EXP(-INDEX('Life tables'!$S$15:$S$115,MATCH(Mortality!$B49,'Life tables'!$B$15:$B$115,0))))`

The yellow highlighted parts of the formula are referring to health states where the CFR, and the age adjustment to the CFR, need to be applied. The formulas look up whether the health state being referred to is either the severe exac (0–3 months) or frequent severe exac (0–3 months),

- And if so, then the CFR is applied (considering the age in column B and applying the relative risk identified from Hoogendoorn linking COPD mortality risk per year of age)
- And if the health state being referred to is not one of the two aforementioned states, then life tables are used for age-based mortality risk (which are the parts of the formula not in yellow above).

B9. In the CS, Section 3.5.2 (page 170) it reads “However, given that few CV [cardiovascular] events were observed across the considered trials, with no meaningful difference between arms reported, and that CV events are unlikely to be a significant driver of model results, CV events were not modelled explicitly, which is likely to be a conservative assumption”. Could the company please provide data on CV events across the trial arms along with their differences?

The data on cardiovascular (CV) events from all three trials, together with the between-arm differences, are presented below.

MATINEE

Overview of adjudicated major adverse cardiovascular event (MACE) (Section 5.2.6.1 CSR)

The total data for the adjudicated MACE analyses showed that the occurrence and risk of Any MACE were similar between the mepolizumab and placebo groups, during both the on-treatment and the on- and post-treatment periods (Table 9).

Table 9: Overview of adjudicated MACE (safety population): MATINEE

Outcome	On- and post-treatment PBO (N=401)	On- and post-treatment Mepo 100 mg (N=403)	On-treatment PBO (N=401)	On-treatment Mepo 100 mg (N=403)
Adjudicated MACE				
Any MACE	██████	██████	██████	██████
CV Death	██████	██████	██████	██████
Non-fatal MI	██████	██████	██████	██████
Non-fatal Stroke	██████	██████	██████	██████
Risk of any MACE				
Relative risk (95% CI)	████████████████		████████████████	

Outcome	On- and post-treatment PBO (N=401)	On- and post-treatment Mepo 100 mg (N=403)	On-treatment PBO (N=401)	On-treatment Mepo 100 mg (N=403)
% risk difference (exact 95% CI)				
Time to first MACE				
First MACE by Week 104, n (%)				
% Probability of a MACE (95% CI) [†]				
HR (mepolizumab / placebo) (95% CI) [‡]				
p-value				

Source: MATINEE CSR, Table 76 (6)

[†]Kaplan-Meier estimate; [‡]Estimated from a Cox Proportional Hazards Model with covariate of treatment group
Abbreviations: CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular event; Mepo, mepolizumab; MI, myocardial infarction; PBO, placebo; RR, relative risk.

METREX

Cardiac disorders (Section 7.2.3.6.1 CSR)

In the overall safety population, on-treatment adverse events (AE) in the Cardiac disorders system organ class (SOC) were reported for █████ participants (████%) in the mepolizumab 100 mg group and █████ participants (████%) in the placebo group. The most frequently reported AEs in this SOC included █████ (████ participants in the mepolizumab 100 mg group and █████ participants in the placebo group), █████ (████ participants in both treatment groups), █████ (████ participants in the mepolizumab 100 mg group and █████ participants in the placebo group), and █████ (████ participants in both treatment groups).

In the overall safety population, serious adverse events (SAE) in the Cardiac disorders SOC were reported for **xx** participants (**x**%) in the mepolizumab 100 mg group and █████ participants (**x**%) in the placebo group. █████ and █████ (████ participants in both treatment groups for each) were reported most frequently. Similar trends for on-treatment AEs and SAEs in the Cardiac disorders SOC were observed between treatment groups in the high stratum and low stratum as in the overall safety population.

Serious cardiac, vascular, and thromboembolic (CVT) events (Section 7.2.3.6.2 CSR)

In the overall safety population, serious on-treatment CVT (including ischemic events) were reported at a similar incidence between the mepolizumab 100 mg (■%) and placebo (■%) treatment groups.

Table 10: Serious on-treatment CVT, cardiac, vascular, respiratory, and nervous system events (safety population)

Event	High Stratum	High Stratum	Low Stratum	Low Stratum	Overall Population	Overall Population
	Placebo N=229	Mepo N=233	Placebo N=190	Mepo N=184	Placebo N=419	Mepo N=417
Any Serious CVT Event						
Any Serious Ischemic Event						
Cardiac disorders						
Atrial fibrillation						
Cardiac failure congestive						
Acute myocardial infarction*						
Cardiac failure						
Cardiac failure chronic						
Palpitations						
Myocardial ischemia*						
Acute coronary syndrome*						
Cardiopulmonary failure						
Sinus tachycardia						
Ventricular tachycardia						
Atrial flutter						
Cardiac arrest						
Cardiac failure acute						
Cardiomyopathy						
Myocardial infarction*						
Bundle branch block left						
Cor pulmonale						
Pericarditis						
Ventricular extrasystoles						
Vascular disorders						
Peripheral ischemia						
Hematoma						
Hypertension						

Event	High Stratum	High Stratum	Low Stratum	Low Stratum	Overall Population	Overall Population
	Placebo N=229	Mepo N=233	Placebo N=190	Mepo N=184	Placebo N=419	Mepo N=417
Hypotension	██████	██████	██████	██████	██████	██████
Orthostatic hypotension	██████	██████	██████	██████	██████	██████
Respiratory, Thoracic & Mediastinal Disorders	██████	██████	██████	██████	██████	██████
Pulmonary embolism	██████	██████	██████	██████	██████	██████
Nervous system disorders	██████	██████	██████	██████	██████	██████
Transient ischemic attack*	██████	██████	██████	██████	██████	██████
Cerebral infarction*	██████	██████	██████	██████	██████	██████

Source: METREX CSR Table 70(7)

Note: Events flagged with an asterisk (*) are serious ischemic events, a subset of serious CVT events, identified via SMQs and sub-SMQs

Abbreviations: CVT, cardiac/vascular/thromboembolic; Mepo, mepolizumab; PE, pulmonary embolism; SC, subcutaneous; SOC, system organ class; TIA, transient ischemic attack.

METREO

Cardiac disorders (Section 7.2.3.6.1 CSR)

On-treatment AEs in the Cardiac disorders SOC were reported for █ participants (█%) in the placebo group, █ participants (█%) in the mepolizumab 100 mg group and █ participants (█%) in the mepolizumab 300 mg group. AEs that occurred with the highest incidence in this SOC included █ (█ participants placebo, █ participants mepolizumab 100 mg, and █ participants mepolizumab 300 mg), █ (█ participants placebo, █ participant mepolizumab 100 mg, and █ participants mepolizumab 300 mg), and sinus tachycardia (█ participants placebo and █ participant mepolizumab 300 mg).

SAEs in the Cardiac disorders SOC were reported for a similar number of participants across the treatment groups: █ participants (█%) in the placebo group, █ participants (█%) in the mepolizumab 100 mg group, and █ participants (█%) in the mepolizumab 300 mg group. █ (█ participants each in the placebo and mepolizumab 100 mg groups) and acute MI (█ participants each in the placebo and mepolizumab 300 mg groups, and █ participant in the mepolizumab 100 mg group) were reported most frequently.

Serious CVT events (Section 7.2.3.6.2 CSR)

Serious CVT (including ischemic events) were reported at similar incidence across the placebo and mepolizumab treatment groups (█%) (Table 11).

Table 11: On-treatment Serious Cardiac, Vascular, and Thromboembolic (CVT) Events including Serious Ischemic Events (Safety Population) (METREO)

Event / SOC Category	METREO		
	Placebo (N=226)	Mepo 100 mg (N=223)	Mepo 300 mg (N=225)
Any Serious CVT Event	█	█	█
Any Serious Ischemic Event	█	█	█
Cardiac Disorders	█	█	█
Atrial fibrillation	█	█	█
Acute myocardial infarction*	█	█	█
Coronary artery disease*	█	█	█
Stress cardiomyopathy*	█	█	█
Supraventricular tachycardia	█	█	█
Acute coronary syndrome*	█	█	█

Event / SOC Category	METREO		
	Placebo (N=226)	Mepo 100 mg (N=223)	Mepo 300 mg (N=225)
Angina pectoris*			
Angina unstable*			
Cardiac arrest			
Cardiac failure congestive			
Cardio-respiratory arrest			
Cor pulmonale			
Myocardial infarction*			
Vascular Disorders			
Aortic aneurysm			
Aortic stenosis			
Essential hypertension			
Hypertension			
Hypertensive crisis			
Hypotension			
Orthostatic hypotension			
Respiratory, Thoracic & Mediastinal Disorders			
Pulmonary embolism			
General Disorders & Administration Site Conditions			
Vascular stent thrombosis			
Nervous System Disorders			
Transient ischemic attack*			

Source: Table 70 METREO CSR(8)

Note: Events flagged with an asterisk (*) are serious ischemic events, a subset of serious CVT events, identified via SMQs and sub-SMQs.

Abbreviations: CV, cardiovascular; CVT, cardiovascular/thromboembolic; MedDRA, Medical Dictionary for Regulatory Activities; MI, myocardial infarction; N, number of subjects; PE, pulmonary embolism; SC, subcutaneous; SMQ, Standardised MedDRA Query; SOC, system organ class.

B10. In the CS, Section 2.8.1 (Figure 10, page 105), the Rate Ratio (RR) for moderate/severe exacerbations in the age group 40-64 years is 0.93, much higher than the RR (reported in Table 52, page 156) used in the company base case analysis. Could the company provide an additional cost-effectiveness scenario analysis based on a cohort with the starting age of 40 years over the lifetime horizon?

Evidence from the trial populations and UK real-world data consistently shows that COPD largely affects older adults (17, 25, 26), which is an important consideration when assessing the validity of an additional scenario analysis in the 40–64 year age group. Within MATINEE (6), around two thirds of the population were in the age group ≥65 years of age, with the mean age being around 66 years. Other relevant randomised controlled trials (RCT) and real-world sources consistently report mean

ages in the mid-to-late sixties e.g. IMPACT (27) mean age of 65.2 years; BOREAS/NOTUS pooled mean age of 65.1 years (in the BOREAS trial 58.1% of participants were aged ≥ 65 years (28), data not reported by age group for NOTUS or BOREA/NOTUS pooled) (29)).

UK RWE also indicates that the COPD population is typically older: Whittaker *et al.*, 2022 (25) (UK Clinical Practice Research Datalink [CPRD]) reports a mean age of 68.2 years among people with COPD (and only around 23% were severe or very severe COPD stage), while the UK NRAP and Outliers data (2021–2023) report median ages in the early seventies (17). Other non-UK real world data such as the DACCORD study in Germany, reported a mean age of 65.7 years (30). Longitudinal CPRD analyses (2000–2019 (26)) and 2004–2023 (25)) also consistently demonstrate increasing prevalence with age. Taken together, these data indicate that people aged 40–64 years comprise a smaller proportion of the real-world population relevant to this appraisal. Modelling a population with a starting age of 40 years and applying treatment effects based solely on data for those aged 40–64 years would therefore not be representative of the population for this appraisal and would not accurately reflect the age distribution observed in clinical trials or UK real-world practice.

Of note, the treatment effect in the model is taken from the pooled mITT-300 trials. In the CS (Table 31), the rate ratio for annualised moderate/severe exacerbations in the overall pooled mITT-300 trial population is 0.84 (0.66, 1.06). Additionally, treatment effect in the 40–64-year subgroup is based on a smaller sample of patients. Basing a scenario solely on data from the 40–64-year subgroup (starting age 40 years and applying the rate ratios estimated for that subgroup) would therefore omit a significant number of trial participants.

However, for completeness, we have provided a scenario analysis using the 40–64-year subgroup data in the model. This scenario analysis uses the data presented in Table 12, Table 13, and Table 14. Age is also updated to 40 years in the model, with the corresponding general population utility values and mortality rates included.

Table 12: Rate ratios of treatment effect on exacerbation rates for mepolizumab vs SoC (MATINEE, METREX, METREO) – 40–64-year-olds

Exacerbation severity	RR (95% CI)	SE
Moderate		
Severe		

Abbreviations: CI, confidence interval; RR, rate ratio; SE, standard error; SoC, standard of care.

Table 13: Composition of response groups (MATINEE) – 40–64-year-olds

Group name	n, ITT	n, responder population	Proportion meeting response criteria (%)
N (evaluable sample size at 1 year)			
On treatment, no exacerbations			
On treatment, ≥1 moderate, but no severe			
On treatment, 1 severe			
On treatment, ≥2 severe			

Abbreviations: ITT, intention to treat.

Table 14: Rate ratios of treatment effect on exacerbation rates for mepolizumab responders vs SoC (MATINEE) – 40–64-year-olds

Exacerbation severity	Rate ratio (95% CI)	SE
Moderate		
Severe		

Abbreviations: CI, confidence interval; SE, standard error; SoC, standard of care.

As previously stated, rate ratios in the 40–64-year-old subgroup are based on lower patient numbers (given that around 60% of the population in the pooled mITT trials were >65 years old) and therefore have wider CIs than the overall population, particularly for the severe exacerbation rates, and also in the responder population. In addition, the underlying assumptions do not align with the characteristics of the population relevant to this appraisal and typically seen in clinical practice. Therefore, results are considered highly uncertain, and of limited value for decision making. Results are presented in Table 16 in Appendix A.

B11. In the CS, Section 3.4.5 (Table 62, page 167). The disutility (-0.034) for ‘Frequent severe (9-12 months)’ is lower than the ‘Frequent severe’ in earlier months. Could the company clarify if this is correct and expected and provide the justification and rationale for this?

The disutility for the frequent severe (9–12 months) health state was based only on one individual (Table 59 of the company submission), therefore there is uncertainty

associated with the disutility for this health state. Alternative sources for disutilities were tested within the scenarios undertaken as part of the company submission and were found to have a negligible impact on results.

For further face validity, a scenario has been undertaken whereby the disutility in the frequent severe (9–12 months) state is set equal to that of the frequent severe (6–9 months) state (see Table 16 in Appendix A), and this had very little impact on the results.

Section C: Textual clarification and additional points

C1. CS Section 3.5.2.2.2, Table 67. Could the company clarify why intensive care unit (ICU) length of stay (LOS) and hospital LOS frequencies are reported differently (i.e., hospital LOS is in days, whereas ICU LOS is expressed as a percentage)? The EAG understands that the hospital LOS of 1 day is applied to 100% of all patients with severe exacerbations. The company model also uses 100% for hospitalisation. Could the company please confirm whether these parameters are reported correctly?

The parameters in Table 67 of the CS are reported correctly. The hospital length of stay (LOS) is presented in days because the model assumes that all patients who experience a severe exacerbation and require hospitalisation will incur at least 1 day in hospital. This assumption is consistent with the MATINEE trial (6), in which a severe exacerbation was defined as one requiring hospitalisation for ≥ 24 hours or resulting in death, thereby supporting the application of a minimum 1-day inpatient stay. In contrast, the intensive care unit (ICU) LOS is reported as a percentage because only a small proportion of hospitalised patients are expected to require ICU care. This approach reflects the method used in the NICE appraisal of dupilumab (12), in which ICU use was reported as the proportion of severe exacerbations involving an ICU stay (around 1%), rather than as a duration applied to all patients.

C2. Appendix B, Section B1.2.1.1 (page 82), second paragraph (just below bullet points) “(dual inhaled therapy with add-ons i.e., LABA+LABA plus a third non-ICS maintenance treatment)” should the second ‘LABA’ be ‘LAMA’?

Yes, that is correct. The second “LABA” in the phrase “dual inhaled therapy with add-ons i.e., LABA+LABA plus a third non-ICS maintenance treatment” is a typographical

error. It should read “LABA+LAMA”. This has been corrected in the updated Appendix B provided in response to C3.

C3. Appendix B. Several of the tables that are referred to in the text appear to refer to the wrong tables in multiple places. For example:

- Section B.1.1.3.1, page 8, the first paragraph refers to Table 1 in the text but from the content and context it appears as if its Table 2 that is being referred to.
- Section B.1.1.4, page 9, second paragraph refers to Table 2 in the text but it is likely to be Table 3 that is really being referred to.
- Section B.1.2.1.2, page 83 the first paragraph refers to Table 1 but it is likely to be referring to Table 19. In the same section in Table 19, page 84 footnote refers to ‘Table 16’ but this does not appear to be the correct table as Table 16 in Appendix B contains an Embase search strategy.

Could the company please submit an updated Appendix B with the correct cross-referencing?

Thank you for highlighting these issues. The cross-referencing throughout Appendix B has now been reviewed in full, and field codes have been updated where required to ensure all table references are correct. The issue noted in C2 has also been corrected. An updated version of Appendix B has been provided alongside the clarification question response.

C4. CS Section 3.3.3.2. The 95% CI for RR reported in text and in Table 52 do not match. Could the company please check and clarify.

Thank you for highlighting this. We have checked the values and can confirm that the rate ratio and 95% CIs reported in the text in the CS were incorrect, while the values presented in Table 52 of the CS were correct (and are confirmed in Table 15, below).

Table 15: RRs for treatment effect on exacerbations, as estimated over the full follow-up, mepolizumab arm vs SoC arm

Exacerbation severity	Pooled mepolizumab Studies*	
	RR (95% CI)	p-value
Moderate exacerbations		
Severe exacerbations		

Abbreviations: CI, Confidence interval; mITT-300, modified intention-to-treat 300 (participants with BEC $\geq$ 300 cells/ μ L at screening who received $\geq$ 1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline; RR, rate ratio.

C5. CS Table 5 (page 52). Please can the company clarify why the trial eligibility criteria for MATINEE, METREX and METREO restricted participants to “*Adults with moderate-to-very severe COPD (GOLD 2–4)*”, yet patients with mild COPD appear to have been included in clinical trials (see CS Table 8 for MATINEE; METREO CSR Table 7 and METREX CSR Table 7) (6-8).

The eligibility criteria for MATINEE (6), METREX (7), and METREO (8) required participants to have moderate-to-very severe COPD (GOLD 2–4) based on pre- and post-bronchodilator FEV₁ assessments performed at the screening visit. No patients with GOLD 1 (mild) COPD were eligible for enrolment, and no such patients were enrolled according to the protocol.

The appearance of a very small number of “mild COPD” patients within the baseline tables (e.g., MATINEE CS Table 8; METREO CS Table 7; METREX CS Table 7) reflects post-hoc central spirometry assessments performed at the baseline visit which can differ slightly from the investigator-performed spirometry used for screening eligibility. To determine eligibility, spirometry was conducted locally at sites and the data were entered into the CRF.

FEV₁ measurements are known to vary between visits due to biological and technical variability. As baseline spirometry was conducted at a different timepoint and analysed centrally for descriptive summaries, a small number of participants whose screening FEV₁ values placed them within GOLD 2–4 may have shifted into an adjacent GOLD stage (including GOLD 1) when categorised for baseline summary purposes.

For statistical analyses, spirometry values undergo central calculation of % predicted FEV₁, which may further contribute to minor differences in GOLD staging compared with screening assessments. These differences are small, expected within the known

variability of FEV₁, and do not indicate protocol deviations nor impact the interpretation of trial results.

Appendix A

Economic model scenario results used within the answers to section B are presented in Table 16.

Table 16: Scenario results

	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER vs. SoC	ICER vs. mepolizumab	Fully incremental ICER	Incr. NHB at £20,000 per QALY (mepolizumab vs. comp)	Incr. NHB at £30,000 per QALY (mepolizumab vs. comp)
Submitted base case									
SoC	██████	██████	–	–	–	–	–	0.07	0.35
Mepolizumab + SoC	██████	██████	██████	██████	£18,347	–	£18,347	–	–
Dupilumab + SoC	██████	██████	██████	██████	£120,738	Dominated	Dominated	3.47	2.39
B1. SMR of 3.85									
SoC	██████	██████	–	–	–	–	–	██████	██████
Mepolizumab + SoC	██████	██████	██████	██████	£20,807	–	£20,807	–	–
Dupilumab + SoC	██████	██████	██████	██████	£142,741	Dominated	Dominated	██████	██████
B2c. Age dependent CFR from NRAP audit using the age adjustment from Samyshkin <i>et al.</i>,									
SoC	xxxxxxx	xxxx	–	–	–	–	–	██████	██████
Mepolizumab + SoC	██████	██████	██████	██████	£18,661	–	£18,661	–	–
Dupilumab + SoC	██████	██████	██████	██████	£124,387	Dominated	Dominated	██████	██████
B3. Dupilumab discontinuation in first year, removing COVID–related discontinuations									
SoC	██████	██████	–	–	–	–	–	██████	██████
Mepolizumab + SoC	██████	██████	██████	██████	£18,347	–	£18,347	–	–
Dupilumab + SoC	██████	██████	██████	██████	£120,671	Dominated	Dominated	██████	██████
B4. 4.58% discontinuation per cycle beyond year 1 (applied to mepolizumab and dupilumab)									
SoC	██████	██████	–	–	–	–	–	██████	██████
Mepolizumab + SoC	██████	██████	██████	██████	£18,645	–	£18,645	–	–
Dupilumab + SoC	██████	██████	██████	██████	£130,449	Dominated	Dominated	██████	██████
B6a. EAG outpatient cost									

	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER vs. SoC	ICER vs. mepolizumab	Fully incremental ICER	Incr. NHB at £20,000 per QALY (mepolizumab vs. comp)	Incr. NHB at £30,000 per QALY (mepolizumab vs. comp)
SoC	██████	██████	–	–	–	–	–	██████	██████
Mepolizumab + SoC	██████	██████	██████	██████	£18,338		£18,338	–	–
Dupilumab + SoC	██████	██████	██████	██████	£120,728	Dominated	Dominated	██████	██████
B6b. Updated global data costs									
SoC	██████	██████	–	–	–	–	–	██████	██████
Mepolizumab + SoC	██████	██████	██████	██████	£18,355	–	£18,355	–	–
Dupilumab + SoC	██████	██████	██████	██████	£120,753	Dominated	Dominated	██████	██████
B10. 40-64-year-old subgroup data									
SoC	██████	██████	–	–	–	–	–	██████	██████
Mepolizumab + SoC	██████	██████	██████	██████	£66,620	–	£66,620	–	–
Dupilumab + SoC	██████	██████	██████	██████	-£216,479	Dominated	Dominated	██████	██████
B11. Disutility in the frequent severe (9–12 months) state is set equal to that of the frequent severe (6-9 months) state									
SoC	██████	██████	–	–	–	–	–	██████	██████
Mepolizumab + SoC	██████	██████	██████	██████	£18,318	–	£18,318	–	–
Dupilumab + SoC	██████	██████	██████	██████	£120,568	Dominated	Dominated	██████	██████

Abbreviations: ICER, incremental cost-effectiveness ratio; Incr, incremental; NHB, net health benefit; QALY, quality-adjusted life year; SoC, standard of care.

Appendix B

Table 17: Summary parameter estimates by distribution

distributio n	Param eter	DF	Estimate	StdErr	LowerC L	UpperC L	ChiSq	ProbChi Sq
exponential	rate	1						
gamma	shape	1						
gamma	rate	1						
gompertz	shape	1						
gompertz	rate	1						
llogistic	shape	1						
llogistic	scale	1						
lnormal	meanlog	1						
lnormal	sdlog	1						
weibull	shape	1						
weibull	scale1	1						

Abbreviations: ChiSq, Chi-squared; CL, confidence limit; DF, degrees of freedom; ProbChiSq, probability of the Chi-square statistic; StdErr, standard error.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Clarification questions – A2 update

18 December 2025

File name	Version	Contains confidential information	Date
ID1237 mepolizumab clarification questions v2.0 [CON]-A2-results	1	No - redacted	18 December 2025

Section A: Clarification on effectiveness data

Indirect Treatment Comparison (ITC)

A2. The analyses conducted to compare trials with individual participant data (IPD) evidence (MATINEE, METREX, and METREO) and aggregate data (NOTUS and BOREAS) utilised a MAIC. However, a multilevel-network meta-regression (ML-NMR) would be more suitable.(1) It appears that adequate covariate data are available from the aggregate data trial for this method to be conducted. As this method does not need to reweight to match across studies, it will lead to increased sample sizes. This method is now accessible using the *multinma* package in R,(2) and is accepted by NICE (see TA1013).(3) Could the company update the analyses with this approach?

Multi-network meta regression (ML-NMR) models have been fitted for the primary endpoint as a supplementary analysis to the MAICs.

In alignment with the methodology applied in the MAICs, ML-NMR models were fitted for both populations:

- Population 1: Defining chronic bronchitis based on investigator assessment (using individual patient-level data [IPD] from the restricted population of the MATINEE trial, and aggregate data from the NOTUS and BOREAS trials)
- Population 2: Defining chronic bronchitis based on Saint George's Respiratory Questionnaire for COPD (SGRQ-C) responses at baseline (using IPD from restricted populations of the MATINEE, METREX, and METREO trials, and aggregate data from the NOTUS and BOREAS trials).

With these three (for Population 1) or five (for Population 2) trials, a network linking studies through placebo as common comparator was established.

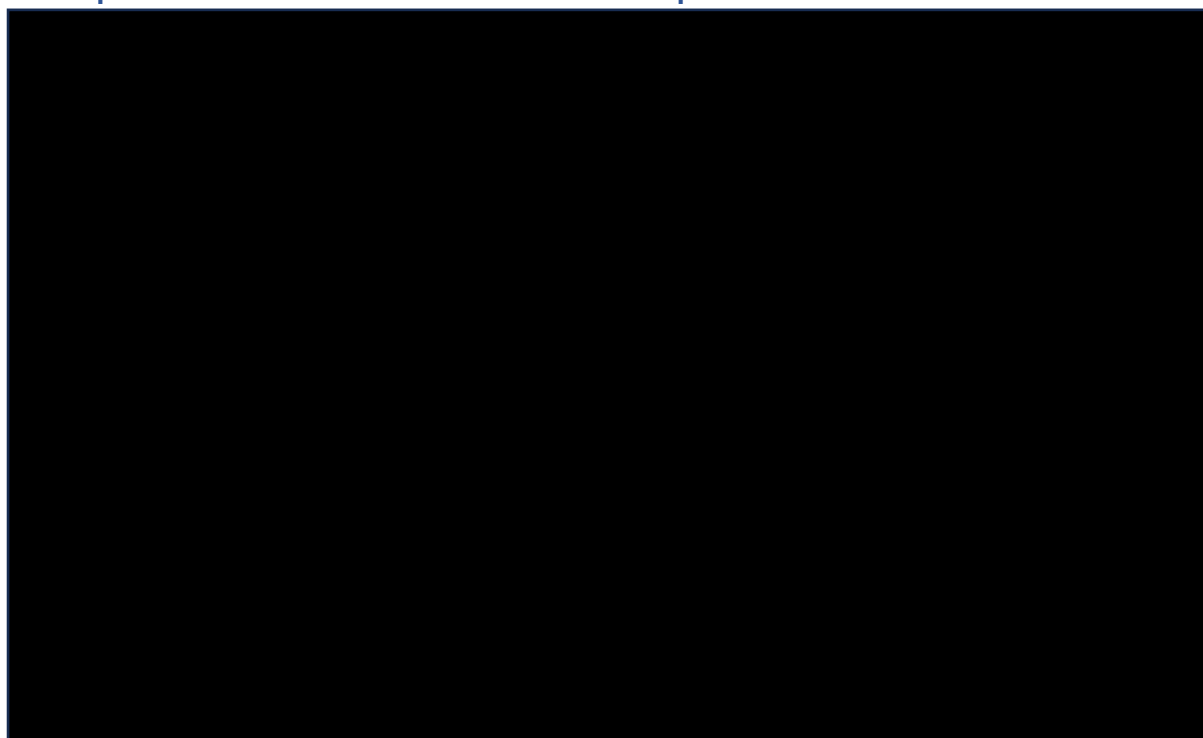
Rates were modelled using observed number of exacerbations and offset terms for each study. Since the negative binomial distribution is not implemented in the *multinma* package in R, the Poisson distribution was used for the underlying data generating model.

The same covariates as in the MAICs were included: Age (in years, numerical), Sex (categorical; male vs. female), Race (categorical; White vs. not White); Geographic region (categorical; Asia vs. Latin America vs. East Europe vs. Western Countries), Body Mass Index (categorical; $<25 \text{ kg/m}^2$ vs. ≥ 25 to $<30 \text{ kg/m}^2$ vs. $\geq 30 \text{ kg/m}^2$), Number of moderate/severe exacerbations at baseline (numerical), Severe exacerbations at baseline (categorical; 0 vs. ≥ 1), Smoking status (categorical; current vs. never/former), Blood eosinophil count at screening (numerical), SGRQ-C total score at baseline (numerical), evaluating respiratory symptoms in COPD (E-RS:COPD) score at baseline (numerical; not collected in METREO/METREX trials so included in the Population 1 analysis only). Covariates were standardised on a common scale to help convergence to the posterior distribution using the Markov Chain Monte Carlo (MCMC) method. The model was fitted using weak, non-informative priors.

As data for dupilumab was only available through aggregate study information and the network is small, we used the shared effect modifier assumption, which assumes that the impact (effect modification) of covariates on treatment effectiveness is the same for the dupilumab and mepolizumab trials in the network, allowing IPD and aggregate data to be synthesised.

Figure 1 summarises the results of the analysis performed for Population 1 and shows the estimated relative treatment effects (expressed as rate ratios on the log scale; with rate ratios and 95% credibility interval added to the right) of all pairs of treatments and in each of the three studies included. As a result of the shared effect modifier assumption, the estimated rate ratio of mepolizumab vs. dupilumab is the same across all studies.

Figure 1: RRs of number of moderate or severe exacerbations estimated from ML-NMR for all pairs of treatments and in all studies – Population 1



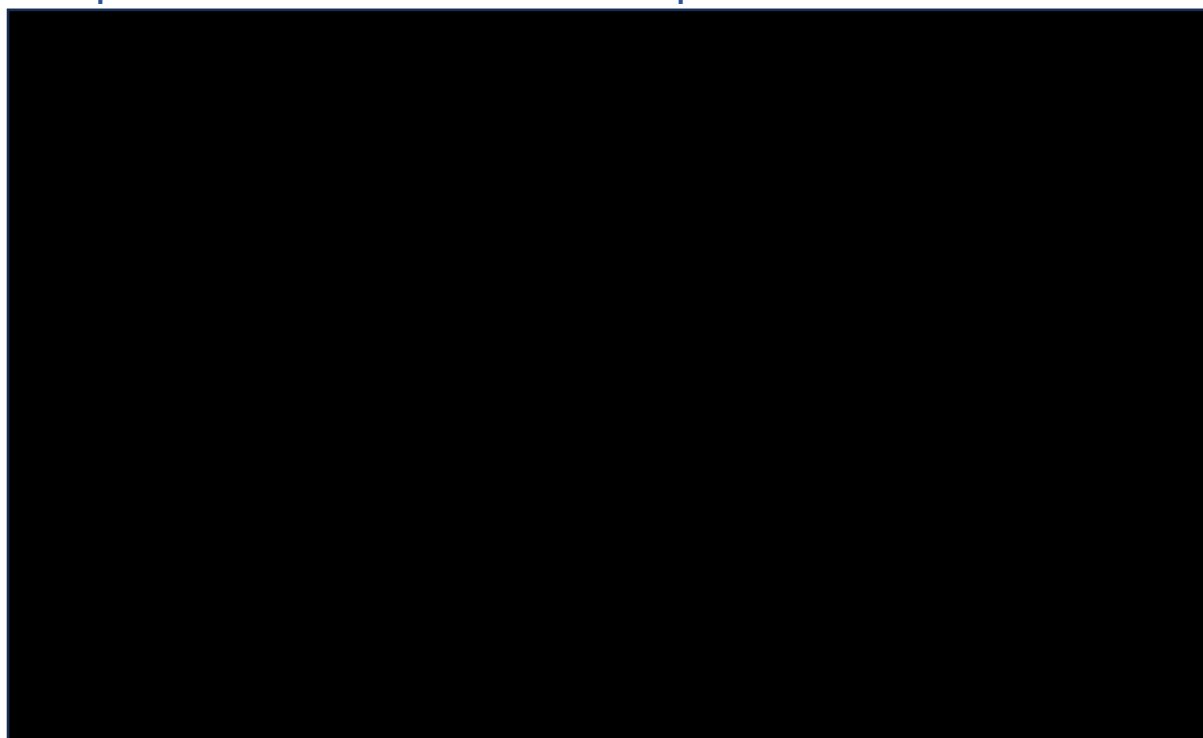
Abbreviations: ML-NMR, multi-level network meta-regression; RR, rate ratio.

The estimated rate ratio of mepolizumab vs. dupilumab in Population 1, adjusting for all covariates listed above, is ■■■■, with the 95% credible interval (CrI) ranging from ■■■■ to ■■■■. For comparison, the respective estimated rate ratio for mepolizumab vs. dupilumab obtained from the MAIC and using a Negative Binomial distribution was ■■■■, with a 95% CrI ranging from ■■■■ to ■■■■. Of note, the 95% CrI in the ML-NMR analysis is substantially wider than the 95% confidence interval (CI) in the MAIC.

Figure 2 summarises the results of the analysis performed for Population 2 and shows the estimated relative treatment effects of all pairs of treatments and in each of the five studies included.

The estimated rate ratio of mepolizumab vs. dupilumab in Population 2, adjusting for all covariates listed above (except E-RS:COPD score), is ■■■■, with the 95% CrI ranging from ■■■■ to ■■■■. For comparison, the respective estimated rate ratio for mepolizumab vs. dupilumab obtained from the MAIC and using a Negative Binomial distribution was ■■■■, with a 95% CrI ranging from ■■■■ to ■■■■.

Figure 2: RRs of number of moderate or severe exacerbations estimated from ML-NMR for all pairs of treatments and in all studies – Population 2



Abbreviations: ML-NMR, multi-level network meta regression; RR, rate ratio.

In summary, results from the ML-NMR are similar to results obtained from the MAICs in both populations (with a higher degree of uncertainty around estimates in the ML-NMR fitted to Population 1), highlighting the robustness of our analyses and the consistency of estimated results across the different methods used.

Scenario analysis

In order to assess the impact of the ML-NMR RR for mepolizumab vs dupilumab on the uncertainty in model results, the updated estimates from the ML-NMR were incorporated into the CEM. Specifically, in the “Tx effect” worksheet, cells T21 to Z21 were updated to reflect the rate ratios and 95% CrI derived from the ML-NMR for moderate/severe exacerbations. Uncertainty was explored through deterministic one-way sensitivity analysis (OWSA) and probabilistic sensitivity analysis (PSA). Please note that the ‘severe exacerbations only’ RR was not revised for this scenario analysis.

Table 1 presents the incremental costs and QALYs and net health benefit (NHB) for mepolizumab vs dupilumab using the ML-NMR results for moderate/severe treatment effect with all other base-case settings held constant. Results are consistent with the

original base case, with only marginal changes in incremental costs and health outcomes vs dupilumab and no material impact on overall conclusions.

The OWSA presented in the CS base case (CS, Figure 15) indicated that moderate/severe exacerbation parameters were not key drivers of model outcomes. While moderate/severe exacerbations appear higher in the ranking relative to the original base case (Figure 3), this does not translate into a meaningful change in results, as severe exacerbations remain the dominant contributor to uncertainty. The OWSA is presented using the incremental NHB, as dupilumab has a dominated incremental cost-effectiveness ratio (ICER) vs mepolizumab.

Consistency in model results is further reflected in the PSA results (Table 2), where dupilumab (at list price) is dominated by mepolizumab in 72.8% of simulations compared to 73.4% in the CS base case. Consequently, the scatter plot and cost-effectiveness acceptability curve (CEAC) show minimal change relative to the base case (Figure 4 and Figure 5). The cost-effectiveness plane remains stable, and decision uncertainty is largely unchanged.

Table 1: Scenario results (deterministic) (mepolizumab PAS price)

	Total costs (£)	Total LYG	Total QALYs	Incr. costs	Incr. LYs	Incr. QALYs	ICER vs. SoC	ICER vs. Mepolizu mab	Fully incremental ICER	NHB 20k (mepolizu mab vs. comp)	NHB 30k (mepolizu mab vs. comp)
CS base case with MAIC results (Population 1)											
SoC	██████	████	████	-	-	-	-	-	-	0.07	0.35
Mepolizu mab + SoC	██████	████	████	██████	████	████	£18,347	-	£18,347	-	-
Dupiluma b + SoC	██████	████	████	██████	████	████	£120,738	Dominated	Dominated	3.47	2.39
CQ A2 scenario base case with ML-NMR results (Population 1)											
SoC	██████	████	████	-	-	-	-	-	-	0.07	0.35
Mepolizu mab + SoC	██████	████	████	██████	████	████	£18,347	-	£18,347	-	-
Dupiluma b + SoC	██████	████	████	██████	████	████	£119,493	Dominated	Dominated	3.47	2.39

Scenario: Treatment effect = ML-NMR moderate/severe exacerbations all other base case inputs held constant

Abbreviations: CQ, clarification question; CS, company submission; ICER, incremental cost effectiveness ratio; Inc, incremental; LYG, life years gained; MAIC, matching adjusted indirect comparison; mepo, mepolizumab; ML-NMR, multi-level network meta regression; NHB, net health benefit; PAS, patient access scheme; QALY, quality adjusted life year; SoC, standard of care; vs, versus

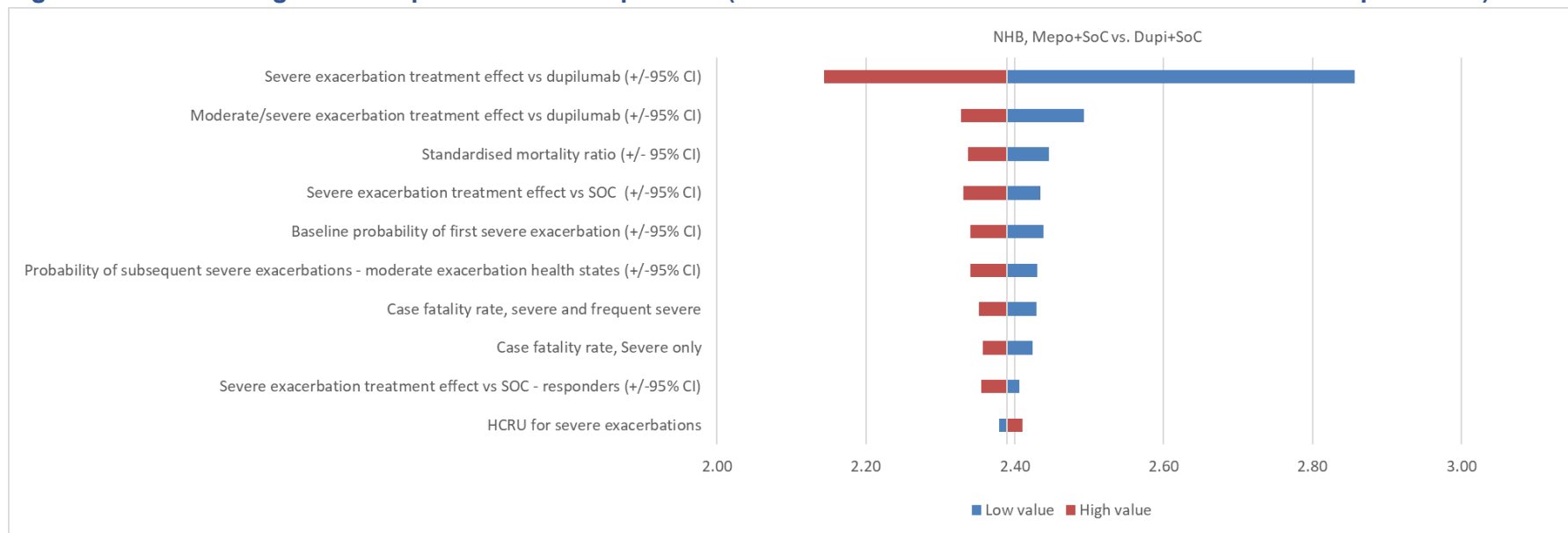
Table 2: Scenario results (probabilistic) (mepolizumab PAS price)

	Total costs (£)	Total LYG (undiscounted)	Total QALYs	Incr. costs	Incr. LYs	Incr. QALYs	ICER vs. SoC	ICER vs. Mepolizumab	Fully incremental ICER	NHB 20k (mepolizumab vs. comp)	NHB 30k (mepolizumab vs. comp)
CS base case with MAIC results (Population 1)											
SoC	██████	████	████	=	=	=	-	-	-	0.07	0.35
Mepolizumab + SoC	██████	████	████	██████	████	████	£18,383	-	£18,383	-	-
Dupilumab + SoC	██████	████	████	██████	████	████	£134,920	Dominate d	Dominate d	3.49	2.43
CQ A2 scenario base case with ML-NMR results (Population 1)											
SoC	██████	████	████	-	████	-	-	-	-	0.07	0.35
Mepolizumab + SoC	██████	████	████	██████	████	████	£18,436	-	£18,436	-	-
Dupilumab + SoC	██████	████	████	██████	████	████	£136,775	Dominate d	Dominate d	3.50	2.44

Scenario: Treatment effect = ML-NMR moderate/severe exacerbations all other base case inputs held constant

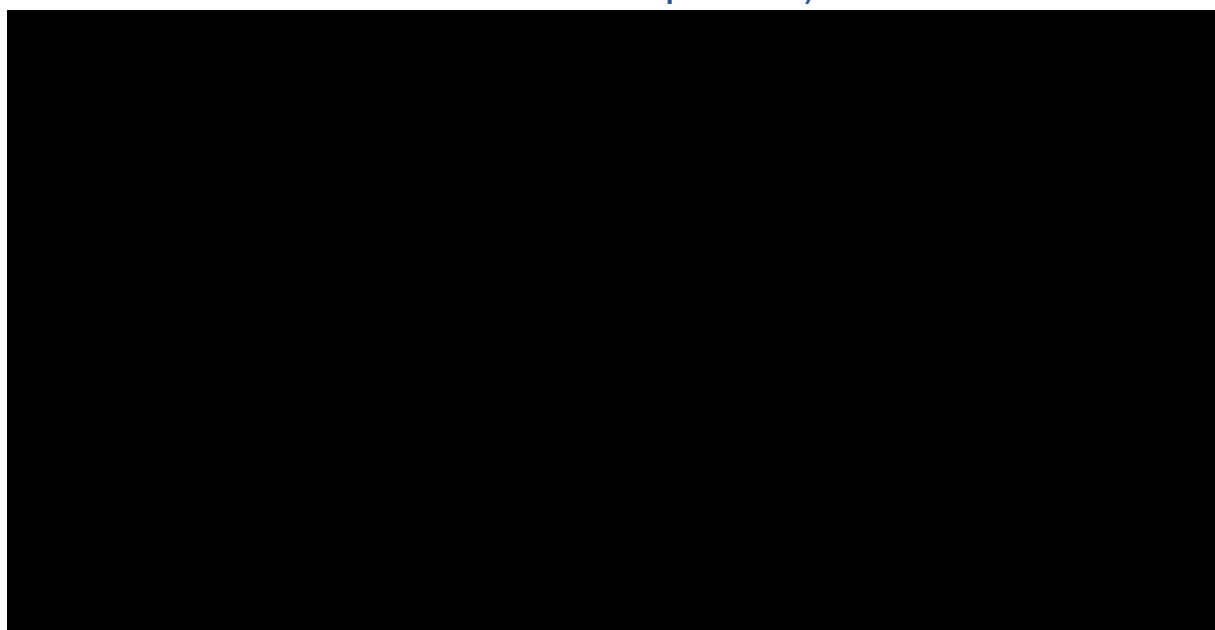
Abbreviations: CQ, clarification question; CS, company submission; ICER, incremental cost effectiveness ratio; Inc, incremental; LYG, life years gained; MAIC, matching adjusted indirect comparison; mepo, mepolizumab; ML-NMR, multi-level network meta regression; NHB, net health benefit; PAS, patient access scheme; QALY, quality adjusted life year; SoC, standard of care; vs, versus

Figure 3: Tornado diagram of mepolizumab vs. dupilumab (CQ A2 scenario base case with ML-NMA results Population 1)



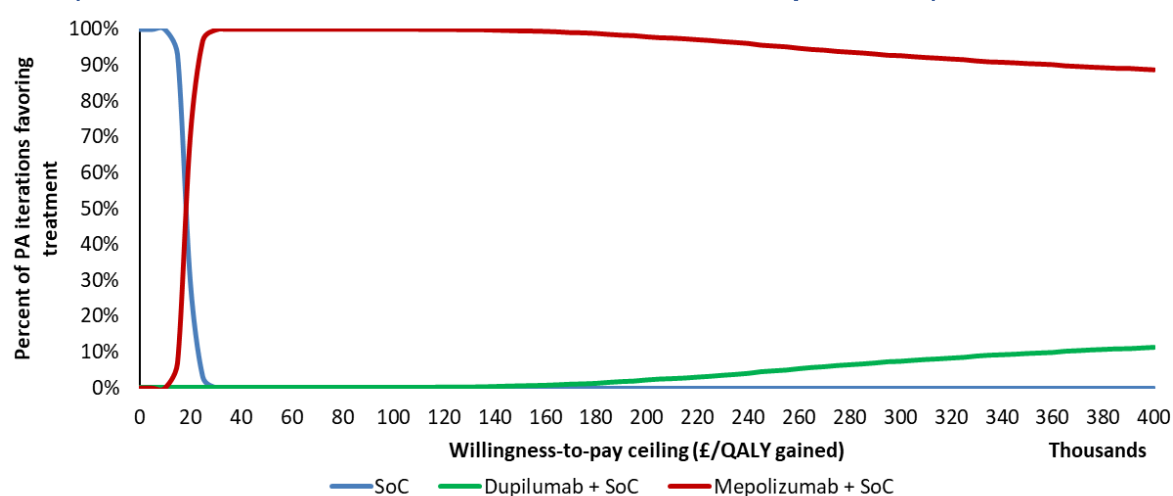
Abbreviations: CI, confidence interval; CQ, clarification question; dupi, dupilumab; HCRU, healthcare resource use; mepo, mepolizumab; ML-NMR, multilevel network meta-regression; NHB, net health benefit; SOC, standard of care.

Figure 4: Cost-effectiveness scatterplot of mepolizumab vs. dupilumab and SoC (CQ A2 scenario base case with ML-NMR results Population 1)



Abbreviations: CQ, clarification question; ML-NMR, multilevel network meta-regression; QALY, quality adjusted life year; SoC, standard of care.

Figure 5: Cost-effectiveness acceptability curve of mepolizumab vs. dupilumab and SoC (CQ A2 scenario base case with ML-NMR results Population 1)



Abbreviations: CQ, clarification question; ML-NMR, multilevel network meta-regression; PA, probabilistic analysis; QALY, quality adjusted life year; SoC, standard of care.

Compared with the equivalent CS scenario analysis, the A2 scenario using the ML-NMR data for the alternative CB definition (SGRQ-C self-report) produces very similar incremental results for mepolizumab versus dupilumab (Table 3).

Table 3: Scenario analysis results vs. dupilumab (deterministic)

Scenario	Incremental costs	Incremental QALYs	Incremental NHB 30K (mepolizumab vs. dupilumab)
CS			
Base case MAIC CB definition (investigator assessed)	██████	██	2.39
Scenario: MAIC CB definition (SGRQ-C self-report)	██████	██	2.25
CQ A2 scenario			
Base case ML-NMR CB definition (investigator assessed)	██████	██	2.39
Scenario: ML-NMR CB definition (SGRQ-C self-report)	██████	██	2.25

Abbreviations: CB, chronic bronchitis; COPD, chronic obstructive pulmonary disorder; MAIC< matching adjusted indirect comparison; ML-NMR, multilevel network meta-regression; NHB, net health benefit; QALY, quality adjusted life year; SGRQ, St George's Respiratory Questionnaire – COPD specific.

Single Technology Appraisal

Mepolizumab for treating chronic obstructive pulmonary disease with an eosinophilic subtype ID1237

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
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- Your response should not be longer than 10 pages.

About you

1. Your name	[REDACTED]
2. Name of organisation	Asthma + Lung UK Taskforce for Lung Health
3. Job title or position	[REDACTED]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Asthma + Lung UK is the nation's lung health charity representing all people across the UK living with a lung condition. Asthma + Lung UK provides the secretariat to the Taskforce for Lung Health. The Taskforce is a coalition of 52 members, including patients, carers, healthcare professionals, the voluntary sector, and professional associations. An Industries Forum, which works alongside the Taskforce, include representatives from the pharmaceutical, diagnostics, devices, and digital industries. The Taskforce for Lung Health receives grants from members of the Industries Forum. The Industries Forum has no editorial control over the Taskforce.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company, the amount, and the purpose of funding.	Sanofi has provided £55,000 in grant funding toward the Taskforce for Lung Health. The Taskforce is funded by its Industries Forum. Sanofi provided £75,000 + VAT toward its COPD Medical Education Roadshow in collaboration with Asthma + Lung UK. Asthma + Lung UK co-branded this initiative, and its policy team members presented to local HCPs across the UK during the roadshow to inspire HCPs to engage with and influence their local policymakers to improve COPD care in their area. AstraZeneca provided £55,000 in funding toward the Taskforce for Lung Health. AstraZeneca provided £150,000 in funding toward Year 2 of the Respiratory Champions programme. GSK provided £55,000 in funding toward the Taskforce for Lung Health. Verona Pharma provided £5,000 in funding toward the Taskforce for Lung Health.

Patient organisation submission

Mepolizumab for treating chronic obstructive pulmonary disease with an eosinophilic subtype ID1237

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	This submission includes patient testimony, which was gathered by discussing these consultation questions in a COPD support A+LUK support group. We also posted a survey on A+LUK's Health Unlocked Forum. In total, 16 patients responded to this survey. This submission also cites Asthma + Lung UK's annual 'Life with a Lung Condition' survey. This survey was open from January to March 2025 and received 9438 responses across the UK.

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	“I am breathless every time I do anything, even, for example, walking from the living room to the kitchen, a journey of only a few yards. After going upstairs, it takes me several minutes to get my breath back. The inability to perform even basic physical functions causes me considerable stress and, at times, depression. My wife is my carer and does almost everything for me. This also, of course, causes me some stress as I feel as though I am just a burden.” - Alan, a patient living with COPD. “I experience breathlessness daily, impacting my ability to do routine tasks. Many times, my breathlessness means I can’t leave the house. I find the symptoms of COPD scary at times, particularly during the winter. In winter, my symptoms are much worse, and I find myself short of breath than usual.” - Doreen, a patient living with COPD. The quotes, from patients from the COPD support group, demonstrate how COPD and the resulting breathlessness profoundly impact patients' lives and their families. Patients with COPD suffer from a range of symptoms, including breathlessness, cough and sputum production, poor sleep, depression, and skeletal muscle loss—such symptom burden can significantly impact people living with COPD’s quality of life. Due to the debilitating symptoms of COPD, in many instances, family members have to act as carers. We hear from patients every day that they feel like a burden to their families, as their breathlessness leads to them needing help to carry out everyday tasks. “I feel very limited in the things I can do now, and I have become very anxious when I am in public in case I get an episode of shortness of breath. I am tired and without energy much of the time and must rest frequently.” - Lily, a patient living with COPD. Many patients with COPD have told us that it can be an isolating disease. It can have devastating consequences on general well-being, with patients feeling hopeless, lonely, and scared. People with COPD are three times more likely to experience loneliness and social isolation than people without COPD.¹ In this year’s ‘Life with Lung Condition’ survey, 63.3% of patients with COPD responded that they feel lonely ‘often’ or ‘some of the time’.² Patients tell us they often feel too anxious to leave the house, due to the fear of having an exacerbation in public. Anxiety and depression are common comorbidities in patients with COPD, with over one in three patients with COPD reporting symptoms of depression and anxiety.³

Patient organisation submission

Mepolizumab for treating chronic obstructive pulmonary disease with an eosinophilic subtype ID1237

	Symptoms of COPD are a significant barrier to patients remaining active and participating in hobbies they used to enjoy. 55% of patients believed their breathlessness affected their ability to exercise,⁴ demonstrating how patients face a life that is compromised through restricted activities. “I find the symptoms of COPD challenging and restricting. I cannot move as quickly up steps and hills. This restricts my activities in work, leisure, and socially.” - David, a patient living with COPD. Patients tell us that due to their COPD symptoms, they have been forced to give up work. 44% of COPD patients are below retirement age, and around one-quarter are not in work due to their COPD.⁵ COPD patients, who are in employment, report having to take more time off and that their breathlessness inhibits their performance at work. Every year, COPD causes reductions in productivity due to illness and premature death, totalling £1.7 billion annually in England.⁶

7. What do patients or carers think of current treatments and care available on the NHS?	“I worry about the side effects of steroid inhalers. I used to love to sing. However, now I can’t sing, as I suffer from a dry mouth. When I broke my arm, I was diagnosed with osteopenia. My rheumatology consultant told me I had developed osteopenia due to taking my high-dose steroid inhaler. They advise me to stop any form of steroid medication, but I have to take a steroid inhaler to manage my breathlessness.” - Felicity, a patient with COPD and patient representative on the Taskforce. Most COPD patients are prescribed an inhaled corticosteroid (ICS) in combination with a bronchodilator. We have heard from patients that they are worried about the side effects of taking high-dose ICS inhalers, with one COPD patient who responded to the survey on the Health Unlocked Forum, suggesting that “without certain medication, my life would be very different now. However, I wish my steroid inhaler didn’t have so many side effects.” Another patient echoed these concerns, telling us that “taking too much of my steroid inhaler brings excruciating leg cramps at night, but what choice do I have?” Patients taking high-dose ICS inhalers are at a higher risk of increased side effects, especially oral candidiasis, dysphonia, pneumonia, and osteoporosis. Long-term ICS use is associated with a 52% increase in the likelihood of developing osteoporosis, so many patients like Felicity (as highlighted above) will suffer from bone density loss.⁷

	Many patients are not confident in the current treatments available, with one patient expressing that “the treatment that I’m on for my COPD doesn’t feel to be particularly effective and every day I struggle with breathlessness.” Another patient who responded to the Health Unlocked Forum survey said: “To be honest, I think my current meds are just like a plaster on a limb amputation.” Others also questioned the effectiveness of their current treatments: “I hardly use my bronchodilator inhaler as it doesn’t seem to do anything.”
8. Is there an unmet need for patients with this condition?	The current therapeutic approach does not meet all the needs of patients with COPD, and for many patients, the available treatments fail to decisively influence the course of the disease.⁸ We have heard from patients who take ICS and bronchodilator inhalers that they are trapped in a vicious cycle of exacerbations and lung function decline. For these patients, there is a huge unmet need, and mepolizumab could be potentially life-changing. People with COPD still struggle to access their essential basic care. A+LUK’s 2025 ‘Life with a Lung Condition’ survey revealed that there is a huge unmet need for COPD patients and that only 8.8% of COPD patients in the UK reported receiving the 5 fundamentals of COPD care (smoking cessation, vaccination, pulmonary rehabilitation, personalised self-management plan, and optimising treatment for co-morbidities).⁹ Only 55% of COPD patients in this annual survey reported being offered stop-smoking cessation support and treatment, a critical intervention to stop the progression of the disease. Only 39% of COPD patients surveyed responded that they have a self-management plan.¹⁰ Self-management plans play a valuable role in supporting people with COPD to manage their condition and respond appropriately to changing symptoms. We are therefore concerned that the majority of COPD patients are not adequately supported to take control of their condition and manage their symptoms. “I would like to complete a course in pulmonary rehabilitation, as I believe it would help me to manage my symptoms. However, I know in my area there are long waiting lists.” - Felicity, a patient living with COPD and a patient representative on the Taskforce. We know that too few COPD patients have access to pulmonary rehabilitation (PR). PR is one of the most cost-effective interventions for COPD, with patients who have completed a course of PR being less likely to be admitted to the hospital. The National COPD Audit found that 76% of people who completed a PR programme avoided hospital admission within six months after their initial assessment, compared to 62.1% who did not.¹¹ PR also reduces the length of hospital stay, with people who were admitted to hospital and had completed a PR

Patient organisation submission

Mepolizumab for treating chronic obstructive pulmonary disease with an eosinophilic subtype ID1237

	course spending only 4.8 days in hospital in six months compared with 9.6 days for those who did not complete the programme.¹² Despite the effectiveness of PR, just 32% of COPD patients in ALUK's 2024 survey reported that they had been offered a course of PR.¹³ Inadequate capacity of PR services in many areas means that once patients are referred, many will sit on a waiting list. Therefore, only 4.3% of the COPD population has completed a course of PR, demonstrating the huge unmet need for patients with COPD.¹⁴ Introducing new drugs to the treatment pathway for COPD patients could be transformative for some patients. Only when basic care needs are met, and care is optimised, can the rest of the unmet needs be met by the introduction of mepolizumab.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	“Biologics give me hope that in the future COPD patients will be able to have more effective treatments, which will give us a better quality of life and reduce the use of high-dose inhalers.” - Alan, a patient living with COPD. Patients living with COPD have told us that biologics, such as mepolizumab, make them hopeful that they will have a “better life quality and will be able to manage this disease.” Another patient, who completed the survey on the Health Unlocked Forum survey, told us they think biologics will “help reduce terrible breathlessness, making walking and doing everyday tasks easier.” Patients have also told us they think an advantage of biologics is that they could reduce their steroid dose, potentially leading to a reduction in adverse side effects. One patient, who responded to the Health Unlocked Form survey, suggested that “a biologic might reduce the amount of steroid I have to use daily or additionally need should I have an exacerbation or lung infection, which would help with reducing the unpleasant side effects I suffer with every day.” Another patient echoed this, telling us that this new drug could allow them to “reduce the frequency I have to take my steroid inhaler, which damages my teeth and gums.” This patient highlighted that, unlike their steroid inhaler, biologics will not leave an unpleasant residue in their mouth. Another patient in the Health Unlocked Forum survey highlighted that a potential advantage of biologics could be “easier to take, as you only have an injection once a month.” Another patient noted that “for me, it would potentially be fantastic as I believe biologics can also help with skin conditions.”

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Patients have told us that a potential disadvantage of biologics is that they may need to attend more hospital appointments. One respondent to the survey on the Health Unlocked Form stated that “the need for a further regular appointment for administration is quite restricting.” Some patients also expressed that they are worried about the financial costs of attending the hospital once a month for the administration of a biologic – a sufficiently designed, inclusive patient pathway would negate this concern, and key lessons on patient accessibility, such as home administration, should be learnt from the severe asthma biologics pathway and the Accelerated Access Consensus pathway for uncontrolled and severe asthma.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	In the clinical trial, mepolizumab decreased the annualised frequency by 20% compared to the placebo.¹⁵ COPD is estimated to account for 1.8 million annual hospital bed days in the UK, with 620,000 occurring during the winter period.¹⁶ Mepolizumab could be particularly beneficial for COPD patients who exacerbate frequently and/ or have frequent exacerbations.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	People from the poorest 10% of households are more than two and a half times more likely to have COPD than someone from the most affluent 10% of households.¹⁷ Poorer people with COPD have more exacerbations, and the poorest people with COPD are being left further behind in terms of the care that they are receiving.¹⁸ Therefore, mepolizumab has the potential to address health inequalities by improving outcomes and quality of life for COPD patients from most of the deprived households.

Other issues

13. Are there any other issues that you would like the committee to consider?	The average age when people are diagnosed with COPD in the UK is 67 years old, and it rarely affects patients under 40 years old.¹⁹ Home administration of biologics for severe asthma patients has worked well, reducing geographical barriers to access. COPD patients are generally older; therefore, it will be important to consider that some may have dexterity limitations and struggle to self-administer injections at home. 86% of COPD patients have at least one comorbidity.²⁰ At the time of diagnosis, the most prevalent comorbidities are mood and anxiety disorders (25.2% for patients with COPD vs 13.1% for patients who do not have COPD).²¹ 15.6% of patients, when they received their COPD diagnosis, had diabetes, 15.5% had peripheral arterial disease, and 13.3% had heart failure.²² The presence of comorbid conditions has important consequences for disease assessment and management. Therefore, the committee must fully consider the interaction between mepolizumab and comorbidities.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• COPD is a devastating condition that impacts all aspects of a patients life. • People living with COPD have been without new treatment options for decades, they are being left behind and are desperate for new, effective treatments to help them live better and longer. • Mepolizumab has the potential to drive improvements in basic care, and support patients better along the entire patient pathway, through optimised care and the 5 fundamental pre-drug eligibility. • Better health will keep people in work, and drive productivity gains for the economy, as well as reducing NHS costs due to COPD exacerbations and hospitalisations. • COPD is a condition driven by inequalities - Mepolizumab has the potential to address health inequalities by improving outcomes and quality of life for COPD patients from most of the deprived households.

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Patient organisation submission

Mepolizumab for treating chronic obstructive pulmonary disease with an eosinophilic subtype ID1237

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- ⁶ Asthma + Lung UK and Taskforce for Lung Health, *Saving your Breath: Technical Report*, (2023) [Accessed here.](#)
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- ⁸ Rosenwasser, Y., Berger, R. and Loewy, Z., *Therapeutic approaches for Chronic Obstructive Pulmonary*, (2022) [Accessed here.](#)
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- ¹⁰ Asthma + Lung UK, *Life with a Lung Condition Survey* (2025). Accessed [here.](#)
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²¹ Skajaa N., Laugesen, K., et al, Comorbidities and mortality among patients with COPD, BMJ Open Respiratory Research (2023). [Accessed here.](#)

²² Skajaa N., Laugesen, K., et al, Comorbidities and mortality among patients with COPD, BMJ Open Respiratory Research (2023). [Accessed here.](#)

Single Technology Appraisal

Mepolizumab for treating chronic obstructive pulmonary disease with an eosinophilic subtype ID1237

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you

1. Your name	
2. Name of organisation	Association of Respiratory Nurses (ARNS)
3. Job title or position	
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Association of Respiratory Nurses (ARNS) was established in 1997 as a nursing forum to champion the specialty respiratory nursing community, promote excellence in practice, and influence respiratory health policy. ARNS also works to influence the direction of respiratory nursing care.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	Yes GlaxoSmithKline - £27,000 + VAT Corporate partnership with ARNS for 2025 and sponsored symposium session at ARNS Conference 2025
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Professional organisation submission

Mepolizumab for treating chronic obstructive pulmonary disease with an eosinophilic subtype ID1237

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Reduce symptoms: relieve symptoms, improve exercise tolerance and improve health status. Reduce risk: Prevent disease progression, prevent and treat exacerbations and reduce mortality.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A clinically significant treatment response may include: Symptom improvement: Reduction in cough, dyspnoea, and phlegm production, with improved exercise tolerance. Physiological improvement: Measurable improvement in lung function parameters. Clinical outcomes: Reduction in the frequency and severity of exacerbations, fewer hospital admissions, and decreased mortality. Quality of life: Demonstrable improvement in patient-reported quality of life and daily functioning.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. • Recognition and management of exacerbations: Improved awareness and earlier recognition of exacerbations by both patients and healthcare professionals to enable timely and appropriate intervention. • Antimicrobial stewardship: Optimising the use of antibiotics during exacerbations to reduce inappropriate prescribing and antimicrobial resistance, while ensuring effective treatment when indicated. • Risk stratification and proactive management: Development and implementation of improved tools to identify and support “rising risk” patients, enabling earlier and targeted interventions. • Patient support and education: Enhanced support to empower patients in self-management, symptom monitoring, and adherence to treatment plans.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Lifestyle and preventive measures: • Smoking cessation support. • Vaccinations (e.g., influenza, pneumococcal, COVID-19). • Promotion of an active lifestyle and participation in pulmonary rehabilitation programmes. Pharmacological management: • Initial pharmacotherapy typically includes dual bronchodilator therapy (LABA/LAMA) or triple therapy (LABA/LAMA/ICS) depending on symptom burden and exacerbation history. • Mucolytics (if suitable) • Consideration of referral for oxygen therapy or long-term antibiotics (if suitable) • Rescue pack (antibiotics and/or steroids) (if suitable) Self-management and education: • Risk factor management • Optimisation of inhaler technique. • Breathlessness management and airway clearance strategies. • Personalised written action plan (or self-management plans) to recognise and manage exacerbations. Comorbidity management: • Active identification and treatment of comorbidities • Consideration of referral for Lung Volume Reduction Surgery (in cases of emphysema)
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE QS 10 NICE NG 114 NICE NG 115 Dupilumab is listed as a comparator but is still under NICE evaluation, which may complicate comparative analysis.

9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	• Diagnosis and access to spirometry: There remains variable access to spirometry in England, which can contribute to delayed or missed diagnoses of COPD. Spirometry and broader lung function testing are currently delivered across Primary, Secondary, and Tertiary care, as well as within Community Diagnostic Centres (CDCs). However, there is ongoing debate across different regions of the UK regarding the most appropriate and efficient setting for accurate diagnosis. • Post-exacerbation review and ongoing management: In Primary care, post-exacerbation reviews and risk stratification are not yet embedded as routine practice. Consequently, patients who experience exacerbations may face delays in receiving guideline-based treatment optimisation, including adjustments to inhaled therapy. • Secondary care management: In Secondary care, patients admitted with COPD exacerbations are generally prioritised for optimisation prior to discharge. However, the availability and consistency of these services vary nationally, leading to unequal standards of post-discharge care and follow-up.
9c. What impact would the technology have on the current pathway of care?	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.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No, as it will rely on home care administration (potentially assisted) whereas current care is self-administered.
10a. How does healthcare resource use differ between the technology and current care?	Self-administered care versus assisted administered care.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This should be used within specialist respiratory clinics in Primary or Secondary care. It should be prescribed and monitored by respiratory healthcare professionals who are confident and competent in its clinical indications. When initiated in Primary care, support and oversight from Secondary care is essential to ensure appropriate patient selection, safe use, and optimal treatment.
10c. What investment is needed to introduce the technology? (For	This will require investment in specialist community respiratory hubs or the development of integrated care pathways that effectively link Primary and Secondary care services. This will support appropriate patient identification, initiation, and follow-up.

example, for facilities, equipment, or training.)	In addition, to also consider: - Establishing an efficient triage system to ensure appropriate and safe prescribing, with clear clinical criteria defining a COPD exacerbation to prevent overprescribing. - Providing training and education for healthcare professionals on patient selection, prescribing protocols, and monitoring within the pathway.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, if it reduces the number of exacerbations and symptom burden that patients experience.
11a. Do you expect the technology to increase length of life more than current care?	Yes, if it reduces the number of exacerbations that patients experience (in the specific raised eosinophil patient group).
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes, if it reduces the number of exacerbations and symptom burden.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The effectiveness and appropriateness of the technology may vary between patient groups: Less effective: This may be less effective in current smokers, as ongoing tobacco use is associated with increased exacerbation risk and progressive decline in lung function. These patients should be prioritised for smoking cessation interventions before or alongside initiation of treatment. More effective: This may be more effective in patients with eosinophilic airway disease, including those with asthma as a comorbid condition. Use of FeNO testing in conjunction with blood eosinophil count may help identify those most likely to benefit. Cost-effectiveness considerations: Given the high cost of biologic therapies, demonstrating incremental cost-effectiveness compared with existing treatments will be critical, particularly in large patient populations.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	This is expected to be equal to current treatments in terms of ease of use for both patients and healthcare professionals. However, additional clinical oversight will be required for patient selection and monitoring, including the potential involvement of a multidisciplinary team (MDT) to assess suitability for treatment. This will require additional clinical time and resource allocation within existing care pathways.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	• Treatment compliance: Ongoing adherence to prescribed therapy should be monitored to ensure effectiveness. • Smoking status: Patients should either have ceased smoking or be actively working towards cessation before or during treatment. • Clinical thresholds: Clear eosinophil count thresholds and exacerbation history criteria should be explicitly defined to identify likely responders and guide continuation or cessation of therapy.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	If successful: • an improved quality of life • less exacerbations.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits	

Professional organisation submission

Mepolizumab for treating chronic obstructive pulmonary disease with an eosinophilic subtype ID1237

and how might it improve the way that current need is met?	
16a. Is the technology a 'step-change' in the management of the condition?	Yes This will offer an opportunity for a new and additional treatment in COPD.
16b. Does the use of the technology address any particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Evidence gaps exist, as the current clinical trials primarily compare mepolizumab to placebo. This may not fully reflect real-world effectiveness or how the treatment performs in comparison to standard care within the UK NHS.
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	

Professional organisation submission

Mepolizumab for treating chronic obstructive pulmonary disease with an eosinophilic subtype ID1237

18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	Foley, T., Smith, D., Quinn, K., Meyer, L., Fest, C., Dodwell, J., ... & DeFranco, F. FDA approves Nucala COPD indication.
21. How do data on real-world experience compare with the trial data?	

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	A potential barrier to equitable access is treatment administration. Patients who are unable to self-administer the therapy and lack family or caregiver support may face challenges in accessing or adhering to treatment. Consideration should be given to providing additional support services or alternative administration options to ensure all eligible patients can benefit.
22b. Consider whether these issues are different from issues with current care and why.	

Topic-specific questions

23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] if there are none delete highlighted rows and renumber below	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	Mepolizumab as an add-on to maintenance treatment could reduce COPD exacerbations, hospitalisations, and urgent care visits, thus improving patient symptom burden and outcomes. Patients should be optimised on existing COPD treatment and lifestyle interventions before initiation. May be most effective in eosinophilic airway disease, and less so in current smokers; clear clinical thresholds are essential for initiation. Implementation requires specialist clinics, integrated care pathways, and healthcare professional education and training, with additional clinical oversight. Equity issues may exist for patients unable to self-administer treatment without support. Ongoing monitoring and multidisciplinary review would be recommended to ensure safe and appropriate use and optimise patient outcomes.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Professional organisation submission

Mepolizumab for treating chronic obstructive pulmonary disease with an eosinophilic subtype ID1237

Single Technology Appraisal

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

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In [part 1](#) we are asking you about living with chronic obstructive pulmonary disease or caring for a patient with chronic obstructive pulmonary disease. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Patient expert statement

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

Please use this questionnaire with our [hints and tips for patient experts](#). You can also refer to the [Patient Organisation submission guide](#). **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Thank you for your time.

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

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Patient expert statement

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

Part 1: Living with this condition or caring for a patient with chronic obstructive pulmonary disease

Table 1 About you, chronic obstructive pulmonary disease, current treatments and equality

1. Your name	Liam Knowles
2. Are you (please tick all that apply)	☒ A patient with chronic obstructive pulmonary disease? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with chronic obstructive pulmonary disease? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Bridges Family and Carers Service
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☒ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☐ I agree with it and will be completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

Patient expert statement

	☐ I have not completed part 2 of the statement
6. What is your experience of living with chronic obstructive pulmonary disease? If you are a carer (for someone with chronic obstructive pulmonary disease) please share your experience of caring for them	I was diagnosed with COPD in my early 40s and am now 47. I manage my condition with Salbutamol and Trelegy inhalers. I have had periods of being prescribed steroids. My symptoms are impacted by weather conditions, winter months can be especially difficult, indoor heating and cold air worsens my breathing. During flare-ups I can struggle to leave the house and often work from home. Severe coughing episodes have previously caused me to lose consciousness due to difficulty catching my breath. COPD impacts my mobility and daily functioning. I run a support service for carers many of whom have COPD.
7a. What do you think of the current treatments and care available for chronic obstructive pulmonary disease on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	When first diagnosed I had steroids in tablet form, which I did not find beneficial and caused weight gain, I believe which made breathing more laboured all round, I have salbutamol for as and when and Trelogy once a day, since moving to that I got improvement. I don't really have much contact with health services, my reviews are once a year and sometimes over the phone, so not much detail gone into. When things get worse, it is difficult to manage and symptoms have usually improved by the time of seeing a clinician, I have been needed urgent care.
8. If there are disadvantages for patients of current NHS treatments for chronic obstructive pulmonary disease (for example, how they are given or taken, side effects of treatment, and any others) please describe these	I found my previous combination of inhalers difficult mainly as I needed to have them with me, cant really get 2 or 3 inhalers in my pocket, if not wearing a big coat, would sometimes drop out of jacket pocket so get left somewhere, if I had my work bag it was ok but I don't always. Also my GP would only let me have one of each when really I could have done with enough to leave one at the office, one in my bag and one at home. I have recently had some jittery episodes which may be due to increased use of salbutamol over winter

Patient expert statement

9a. If there are advantages of mepolizumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does mepolizumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	I have no experience of mepolizumab But something through longlasting injecting would make improvements and would also prevent things getting worse rather than treating an attack once it occurs, also not requiring additional medications or inhalers Preventing escalation, would reduce distress, and avoid urgent medical attention being needed I think it would reduce the need for admissions, or appointments with doctor, while not requiring people to remember to take anything extra multiple times per day
10. If there are disadvantages of mepolizumab over current treatments on the NHS please describe these. For example, are there any risks with mepolizumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Just that it does not replace existing treatment and is an extra
11. Are there any groups of patients who might benefit more from mepolizumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Those with acquired brain injury, cognitive or memory impairments by not requiring them to remember to keep up medication schedules if prescribed additional People who just find it difficult organise, their own treatment Dexterity, avoiding fiddly tablets, or inhaler some of which require certain handling Anything which can prevent, saves people trying to get seen by clinician and also benefits health service by reducing pressure Mobility could be an issue if people are required to attend once every 4 weeks People with busy lives can sometimes be disadvantaged by routine appointments with lack of flexibility of appointments, weekends or out of hours

Patient expert statement

12. Are there any potential equality issues that should be taken into account when considering chronic obstructive pulmonary disease and mepolizumab? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	I am not sure of any other than COPD is still seen too often as something impacting the elderly,
13. Are there any other issues that you would like the committee to consider?	no

Patient expert statement

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

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Something that prevents escalation is good
- Minimising pressures of adhering to medication
- Longlasting Injections make things easy
- Appointments should be available out of hours
- Always having multiple inhalers 'just in case' is more difficult than people think

Thank you for your time.

Your privacy

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Patient expert statement

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

Single Technology Appraisal

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

Clinical expert statement

Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

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Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Clinical expert statement

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

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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Clinical expert statement

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

Part 1: Treating chronic obstructive pulmonary disease and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Richard Russell
2. Name of organisation	King;s College London, Hampshire Isle of Wight NHS trust
3. Job title or position	
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with chronic obstructive pulmonary disease? ☒ A specialist in the clinical evidence base for chronic obstructive pulmonary disease or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil to disclose
8. What is the main aim of treatment	To reduce the number of exacerbations of COPD

Clinical expert statement

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

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A reduction of 1 event a year would be significant for an individual, as a group mean this may well be approximately a 20% reduction based on group risk.
10. In your view, is there an unmet need for patients and healthcare professionals in chronic obstructive pulmonary disease?	Yes, patients with COPD continue to have exacerbations in spite of optimal therapy. These events have impact at every level: patient, family, healthcare providers, payers and society as a whole.
11. How is chronic obstructive pulmonary disease currently treated in the NHS? - Are any clinical guidelines used in the treatment of the condition, and if so, which? - Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) - What impact would the technology have on the current pathway of care?	NICE guidelines Local COPD Guidelines GOLD strategy We now have a COPD biologics commissioning template and recommendations from NHSE which does outline a clear pathway. There is a large variation of care across the UK which varies from area to area and is often driven by deprivation as well as variable service provision. Opinion does not differ, but provision does. The impact as a disruptor would enable a reset of services and focus us on the provision of care fundamentals as well as new technologies such as this.,
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? - How does healthcare resource use differ between the technology and current care? - In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	No, this is new technology and a completely novel therapy for COPD patients. It adds on to current care which is inadequate and addresses both the clinical need and the government's healthcare priorities This therapy should be used in the patient's neighbourhood and is amenable to home care. This therapy will address and enable: Prevention rather than treatment Neighbourhood rather than secondary care

Clinical expert statement

What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Data will be collected with patient selection made using digital methods and the therapy will enable a significant levelling up agenda and a reduction in health inequality. Investment will be needed in data collection and audit which will enable appropriate governance. No equipment is necessary and home care can be the method of delivery.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? - Do you expect the technology to increase length of life more than current care? - Do you expect the technology to increase health-related quality of life more than current care?	Yes, the studies have shown a reduction in exacerbation rate of 20% on top of standard of care. Exacerbations cause death and disease progression. Thus there will be a reduction in mortality as well as a reduction in cost through reduced healthcare utilisation. This new therapy is on top of current standard of care which is not adequate for patients to prevent exacerbations.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	COPD patients with raised blood eosinophil counts (eos >300 especially) and a history of exacerbations (1 or more in the last year) will benefit most. This is about 14% of COPD population.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Easier: an injection rather than inhalers. Can be delivered by homecare and self administered. Long acting depo is also coming.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No, all patients have had a full blood count in their history. Start if having exacerbations on current standard of care. Stop if exacerbations continue.

Clinical expert statement

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

17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Yes, this will be due to overall reduction in health care costs, benefits to carers and family, time at work for both patients (25% of hospital admissions for COPD are younger than 65) and also reduction in exacerbation induced cardiac disease and steroid induced long term morbidity (repeated use of oral steroids leads to: hypertension, diabetes, osteoporosis, sarcopenia etc) all with costs.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	Yes as a disruptor this tech enables COPD pathways to review the effective and high value fundamentals of care (Smoking cessation, pulmonary rehab., oxygen review) and effective inhaled therapies. This will raise standards everywhere and enable commissioners to drive effective care pathways for COPD. Also England is not doing enough lung transplantations and this is due to not enough people being referred, a revision of pathways will enable the question to be asked about the role and potential of transplantation in patients who are currently missed. Unmet need of continued exacerbations as well as inequitable care.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	No issues
20. Do the clinical trials on the technology reflect current UK clinical practice? - If not, how could the results be extrapolated to the UK setting? - What, in your view, are the most important outcomes, and were they measured in the trials?	Yes, as the entry criteria for the study does represent current standard of care. Exacerbation rates are the most important outcome and reflect a need. Of course this is one metric (as an RCT driven by FDA defined outcomes). We need to collect data on every patient treated in a national registry and follow their outcomes to best measure real life efficacy. Of course long term safety monitoring will be an essential part of this.

Clinical expert statement

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No, other than some patients may have been treated in the past with an asthma diagnosis who in reality have COPD and so there may be some data that can be collected in this manner. Not done as yet.
23. How do data on real-world experience compare with the trial data?	Unknown. Data from other countries with similar drugs (Dupilumab) from Israel and China have demonstrated outcomes better than the RCT.
24. NICE considers whether there are any equality issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population	Deprivation is a huge driver of inequality in COPD. This is an opportunity to address this. Those with the greatest deprivation have the most exacerbations, have the most hospital admissions and cost the most to the NHS. This new therapy is a way of changing our approach and reaching these populations in order to prevent disease.

Clinical expert statement

- lead to recommendations that have an adverse impact on disabled people.

Please consider whether these issues are different from issues with current care and why.

More information on how NICE deals with equalities issues can be found in the [NICE equality scheme](#).

[Find more general information about the Equality Act and equalities issues here.](#)

Clinical expert statement

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

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

1. Current COPD therapy is inadequate and does not prevent exacerbations in a significant population.
2. This population is easy to recognise, detect in primary care and treat with Mepolizumab in primary care.
3. As a new therapy there is an opportunity to reassess COPD pathways from diagnosis to complete treatment.
4. This new therapy aligns with the need to treat in the community (Neighbourhood) and be focussed on optimal therapy to prevent events as well as treat all equally.
5. COPD affects a large proportion of the UK population and causes significant morbidity, premature mortality and cost affecting patients, family, carers, health care providers, hospital beds (major driver of winter bed crises) and society as a whole, reducing exacerbation rates will reduce this burden of disease.

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Clinical expert statement

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

External Assessment Group (EAG) Report

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

Produced by
Authors

Newcastle University
Louise Tanner, Research Associate
Nawaraj Bhattarai, Senior Research Associate
Sonia Garcia Gonzalez-Moral, Research Associate
Lakshmi Jayachandran, Research Associate
Sheila A Wallace, Research Fellow
Kate Lanyi, Research Associate
Julia Whitehall, Research Associate
Oleta Williams, Research Assistant
Ryan PW Kenny, Senior Research Associate
Asra Asgharzadeh, Senior Research Associate
Gurdeep S Sagoo, Senior Lecturer
Gill Norman, Principal Research Associate
Katie H Thomson, Senior Research Associate

Correspondence to

Katie Thomson, Newcastle University
Population Health Sciences Institute,
The Catalyst, Room 3.12, 3 Science Square
Newcastle Helix, Newcastle upon Tyne, NE4 5TG

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Rider on responsibility for report

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Contributions of authors

Louise Tanner led the clinical effectiveness, wrote Sections of the clinical effectiveness assessment and edited the report.

Sonia Garcia Gonzalez-Moral, Kate Lanyi and Sheila Wallace acted as clinical effectiveness reviewers, wrote Sections of the clinical effectiveness assessment and edited the report.

Oleta Williams reviewed the literature search methods, wrote the search-related Sections of the report and edited the report.

Julia Whitehall and Ryan Kenny acted as clinical effectiveness and cost-effectiveness reviewers, wrote Sections of the clinical effectiveness and cost-effectiveness assessment and edited the report.

Lakshmi Jayachandran wrote Sections of the health economics assessment and undertook economic modelling.

Nawaraj Bhattarai led the health economics, wrote Sections of the health economics assessment, undertook health economic modelling and edited the report.

Gurdeep Sagoo and Asra Asgharzadeh provided advice on the economic model and commented on the report.

Gill Norman provided clinical effectiveness support, edited the report and acted as project co-lead.

Katie Thomson provided clinical effectiveness support, wrote Sections of the clinical effectiveness assessment, edited the report and acted as project co-lead.

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Report key:

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Table of Contents

1	Executive summary	15
1.1	Overview of EAG's key issues	15
1.2	Overview of key model outcomes	15
1.3	EAG's key issues	17
1.4	Secondary issues identified by the EAG	17
1.5	Company's modelling errors identified by the EAG	23
1.6	Summary of EAG's preferred assumptions and resulting ICER.....	24
1.7	Outline of confidential comparator or subsequent treatment prices ..	27
2	Background	27
2.1	Critique of the Company's description of underlying health problem	27
2.1.1	Burden of disease.....	28
2.2	Critique of the Company's overview of current service provision	32
2.2.1	Treatment guidelines.....	34
2.2.2	Unmet need	35
2.2.3	Positioning of mepolizumab in the care pathway	37
2.2.4	Equality considerations	38
2.3	Critique of the Company's definition of decision problem	41
2.3.1	Population	49
2.3.2	Comparators	52
2.3.3	Outcomes	54
3	Clinical effectiveness.....	55
3.1	Critique of the methods of the review.....	56
3.1.1	Search strategies.....	59
3.1.2	Search filters	59
3.1.3	Eligibility criteria.....	60
3.1.4	Study selection	61
3.1.5	Evidence review.....	62
3.2	Critique of the methods of the trials for the technology of interest	64
3.2.1	Eligibility criteria.....	80
3.2.2	Randomisation and statistical analyses	81

3.3	Critique of the results of the trials of the technology of interest.....	83
3.3.1	Baseline characteristics.....	98
3.3.2	Drop-out rate	102
3.3.3	Primary efficacy outcome	102
3.3.4	Secondary exacerbation outcomes.....	103
3.3.5	AEs.....	103
3.3.6	HRQoL outcomes	103
3.3.7	Subgroups.....	105
3.4	Critique of studies identified and included in the indirect treatment comparison or multiple treatment comparison.....	109
3.4.1	Randomisation.....	122
3.4.2	Lung function, mortality and adverse effects of treatment.....	122
3.5	Critique of the Indirect Treatment Comparisons (ITCs).....	122
3.5.1	Statistical analysis.....	131
3.5.2	Transitivity.....	132
3.5.3	Results and sensitivity analyses.....	134
3.6	Additional work on clinical effectiveness done by the EAG	137
3.7	Conclusions of the clinical-effectiveness Section.....	137
3.7.1	Conclusions of the clinical effectiveness SLR.....	137
3.7.2	Conclusions on the MATINEE, METREX and METREO trials	138
3.7.3	Conclusions on the ITCs.....	141
4	Cost effectiveness	142
4.1	Critique of the review of cost-effectiveness evidence.....	142
4.1.1	Search methods.....	145
4.1.2	Eligibility criteria.....	146
4.1.3	Study selection	147
4.1.4	Evidence review.....	148
4.2	Critique of the submitted economic evaluation	150
4.2.1	NICE reference case checklist.....	150
4.2.2	Model structure.....	152
4.2.3	Population	155
4.2.4	Intervention and comparators	157

4.2.5	Treatment effectiveness and extrapolation	159
4.2.6	Treatment discontinuation.....	169
4.2.7	Mortality.....	173
4.2.8	Health-related quality of life.....	176
4.2.9	Resources and costs.....	179
4.3	Company's cost-effectiveness result.....	195
4.3.1	Company base-case	195
4.3.2	Company sensitivity and scenario analysis.....	197
4.3.3	Model validation and face validity check.....	211
4.4	EAG's additional analyses	212
4.4.1	EAG's preferred assumptions	212
4.4.2	Additional scenario analyses conducted by the EAG	212
4.5	Conclusions of the cost-effectiveness section	216
5	References.....	219
6	Appendix.....	231



Table of figures

Figure 3.1: Annualised rate of moderate/severe exacerbations by subgroup (MATINEE).....	107
Figure 4.1: Model structure in the Company submission.....	153
Figure 4.2: Company base-case CE plane.....	200
Figure 4.3: Company base-case cost-effectiveness acceptability curve (CEAC) ...	201
Figure 4.4: Tornado diagram illustrating top 10 drivers of variance around the ICERs (mepolizumab + SoC versus SoC)	203
Figure 4.5: Tornado diagram illustrating top 10 drivers of variance around NHB (mepolizumab + SoC versus dupilumab + SoC)	204

Table of tables

Table 1:1: List of EAG exploratory analyses on Company base-case.....	24
Table 1:2: Deterministic results of EAG's exploratory analyses using Company's base-case model – mepolizumab + SoC versus SoC	26
Table 1:3: Deterministic results of EAG's exploratory analyses using Company's base-case – mepolizumab + SoC versus dupilumab +SoC	26
Table 2:1: Summary of the EAG critique of the Company's description of the condition.....	27
Table 2:2: Summary of the EAG critique of the Company's overview of current service provision	32
Table 2:3: Summary of the decision problem	41
Table 2:4: COPD Staging.....	51
Table 3:1: Summary of the EAG's critique of the methods implemented by the Company to conduct the SLR	56
Table 3:2: Summary of EAG's critique of the MATINEE, METREO, METREX and mITT-300 pooled analysis methods	66
Table 3:3: Summary of MATINEE methods critique.....	67
Table 3:4: Summary of METREO methods critique	71
Table 3:5: Summary of METREX methods critique.....	74
Table 3:6: Summary of EAG's assessment of trial results.....	83
Table 3:7: Summary of Company interpretation of MATINEE trial results.....	85
Table 3:8: Summary of Company interpretation of METREX trial results.....	89
Table 3:9: Summary of Company interpretation of METREO trial results	92
Table 3:10: Summary of Company interpretation of mITT - 300 pooled analyses trial results.....	96
Table 3:11: MATINEE participant baseline characteristics up to 52 weeks fixed duration and 104 weeks variable duration (mITT population).....	100
Table 3:12: Summary of NOTUS and BOREAS methods critique	110
Table 3:13 Summary of EAGs interpretation of BOREAS and NOTUS trial results	116
Table 3:14: Summary of the EAG's critique of the Company's ITCs	125
Table 3:15: Summary of participant numbers and study dates for trials included in the ITC analyses (before matching).	133
Table 4:1: Summary of the EAG'S critique of the methods implemented by the Company to conduct the economic systematic literature review	142
Table 4:2: NICE reference case checklist	150
Table 4:3: Baseline characteristics of patient population in the Company base-case.	156
Table 4:4 Proportion of responders to mepolizumab and dupilumab used in the Company's base-case model	160
Table 4:5: Background therapy first exacerbation rates used in the Company's model (base-case and scenario analysis)	161
Table 4:6: Rate Ratios for subsequent exacerbations in the Company's economic model	162
Table 4:7: Treatment effect for exacerbation rates, mepolizumab vs background therapy (base-case and scenario analyses) used in Company's economic model	163

Table 4:8: Treatment effect for exacerbation rates, mepolizumab vs dupilumab used in the Company's economic model.....	164
Table 4:9: Rate Ratios for exacerbations in responders used in the Company's economic model	168
Table 4:10: Probability of treatment discontinuation for mepolizumab in Year1 of Company's base-case economic model.....	169
Table 4:11: Probability of treatment discontinuation mepolizumab in Year 2 of the Company's base-case economic model.....	170
Table 4:12: Utility values used in the Company base-case	177
Table 4:13: Disutility values used for scenario analysis in the Company's economic model.	178
Table 4:14: Acquisition costs for intervention and comparator treatments used in the Company's economic model	182
Table 4:15: COPD management costs applied in the Company's base-case economic model	183
Table 4:16: Moderate exacerbation resource use costs used in the Company's economic model	186
Table 4:17: Severe exacerbation resource use and costs used in the Company's base-case economic model.....	188
Table 4:18: Company's model inputs for productivity loss.....	191
Table 4:19: Company's model inputs for early retirement loss	192
Table 4:20: Deterministic Company's base-case incremental analysis	196
Table 4:21: Deterministic Company's base-case NHB and NMB	196
Table 4:22: Company's probabilistic incremental cost-effectiveness result.....	199
Table 4:23: Company's probabilistic NHB and NMB result	199
Table 4:24: Company's one-way sensitivity analysis results, mepolizumab + SoC versus SoC.....	202
Table 4:25: Scenarios explored by the Company.....	205
Table 4:26: Company's scenario analysis results for mepolizumab versus SoC....	206
Table 4:27: Company's scenario analysis results for mepolizumab versus dupilumab	207
Table 4:28: Company's additional scenarios after EAG's PfC ¹²	209
Table 4:29: Company' additional scenario results for mepolizumab versus SoC ...	210
Table 4:30: Company's additional scenario results for mepolizumab versus dupilumab.....	210
Table 4:31: Additional scenario analyses conducted by the EAG	212
Table 4:32: EAG's additional scenario results (mepolizumab + SoC versus SoC).	216
Table 4:33: EAG's additional scenario results (mepolizumab + SoC versus dupilumab + SoC)	216

Abbreviations

AD	Active disease
AE	Adverse events
A&E	Accident and emergency
AESI	Adverse event of special interest
AIC	Akaike's Information Criterion
ARNS	Association of Respiratory Nurses
ATS	American Thoracic Society
BCC	Best care COPD program
BEC	Blood eosinophil count
BI	Budget impact
BID	Twice daily
BIC	Bayesian information criterion
BSA	Body surface area
BMI	Body mass index
BSR	British Society for Rheumatology
CDA	Canadian Agency for Drugs and Technologies in Health, CADTH)
CAT	COPD Assessment Test
CB	Chronic Bronchitis
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CFB	Change from baseline
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CKD	Chronic kidney disease
CMID	Clinically meaningful important difference
COI	Cost of illness
CONSORT	Consolidated Standards or Reporting Trials
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease

CPAP	Continuous positive airway pressure
CPRD	Clinical Practice Research Datalink
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company's submission
CSR	Clinical study report
CFR	Case fatality ratio
CT	Computerised tomography
CUA	Cost-utility analysis
DC	Date created
DD	Date dependent
DSU	Decision Support Unit
EAG	External Assessment Group
ED	Emergency department
ERS	European Respiratory Society
E-RS: COPD	Exacerbations of COPD Tool – Respiratory Symptoms
ESS	Effective sample size
FDA	Food and Drug Administration
FEV ₁	Forced expiratory volume in one second
FeNO	Fractional exhaled nitric oxide
FVC	Forced vital capacity
GERD	Gastrooesophageal Reflux Disease
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General practitioner
HCRU	Health care resource use
HRQoL	Health-related quality of life
HTA	Health technology assessment
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
ICS	Inhaled corticosteroids
IL	Interleukin
ITC	Indirect treatment comparison

ITT	Intention-to-treat
IV	Intravenous
IVC	Intravenous cyclophosphamide
IWRD	Interactive web response system
Kg/m ²	Kilogram per square meter
KM	Kaplan-Meier
LABA	Long-acting Beta agonists
LAMA	Long-acting muscarinic antagonists
LB	Lower bound
LS	Least square
LY	Life year
LYG	Life years gained
MAIC	Matching-adjusted indirect comparison
MeSH	Medical subject headings
ML-NMR	Multilevel network meta-regression
mITT	Modified intention-to-treat
mMRC	Modified Medical Research Council
μL	Microlitre
mg	Milligram
NA	Not applicable
NHB	Net health benefit
NHS	National Health Service
NMB	Net monetary benefit
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NR	Not reported
NRAP	National Respiratory Audit Programme
OCS	Oral corticosteroids
OHID	Office for Health Improvement and Disparities
OR	Odds Ratio
ONS	Office for National Statistics
PAS	Patient access scheme

PBO	Placebo
PfC	Points for Clarification
PICOS	Population, Intervention, Comparison, Outcomes
ppb	Parts per billion
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PROSPERO	Prospective Register of Systematic Reviews
PRR	Partial renal response
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q2W	Every 2 weeks
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RR	Rate ratio
SC	Sub-cutaneous
SAE	Serious adverse events
SD	Standard deviation
SE	Standard error
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SMR	Standardised mortality ratio
STA	Single Technology Appraisal
SGRQ	St George's Respiratory Questionnaire
SoC	Standard of Care
TA	Technology Assessment
TAC	Tacrolimus
TEAE	Treatment emergent adverse events
TTO	Time trade-off

TTOT	Time-to-off treatment
UK	United Kingdom
ULN	Upper limit of normal
USA	United States of America
VOC	Voclosporin
WHO	World Health Organization
WTP	Willingness-to-pay

1 Executive summary

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Section 1.3 explains the key issues in more detail. Secondary issues and modelling errors identified by the EAG are explored in Sections 1.4 and 1.5. Background information on the condition, technology and evidence, and non-key issues are presented in later Sections of the EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of EAG's key issues

The EAG have not identified any key issues. Secondary issues which the EAG have identified are summarised in Section 1.4.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a QALY. An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled in the Company's base-case analysis to affect QALYs by:

- The risk of moderate/severe exacerbations in patients, which is determined by the comparative treatment effect (rate ratio) that reduces the annualised rate (rate ratios) of moderate/severe exacerbations, as well as the baseline exacerbation rates. The moderate/severe exacerbations have significant negative impact on the health-related quality of life (HRQoL) of chronic obstructive pulmonary disease (COPD) patients.

- The proportion of responders to the treatment at the end of year 1, who continue to receive the treatment, have reduced risk of exacerbations and therefore, improved subsequent HRQoL.

Overall, the technology is modelled to affect costs by:

- Variations in the proportion of patients that undergo treatment discontinuation that directly affects the treatment costs in the model. An increase in treatment discontinuation reduces the total cost of the treatment and vice versa.

The modelling assumptions that have the greatest impact on the ICER are:

- Exacerbations are the most important health outcome determinant. Therefore, changes in the exacerbation (moderate and severe) rates have significant impact on both costs and QALYs, and subsequently on the ICER.
- Severe exacerbations have more detrimental impact on the patient outcomes compared to moderate exacerbations. These require hospitalisation, treatments to manage the symptoms, and are associated with additional resource utilisation, which would result in increased total cost. The patients also experience significant worsening of their quality of life during a severe exacerbation and do not revert to their original baseline health even after this episode.
- The submission assumes that the target population is older (informed by evidence, to reflect the UK COPD population) and the corresponding treatment effects were used in the model. However, a treatment effect estimate (higher than the input in the Company base-case) corresponding to a younger population (which was informed by trial data) resulted in a significantly higher ICER. Hence, treatment effect (related to age) is a parameter that has a high impact on the ICER.

1.3 EAG's key issues

The EAG have not identified any key issues in this submission.

1.4 Secondary issues identified by the EAG

The following section highlights secondary issues that the EAG believes to represent areas of uncertainty but have a less significant impact than the issues identified in Section 1.3.

Issue 1: Ensure universal access to the five fundamentals of care specified in the NICE guidelines for COPD (NG115)¹

Report Section	Text
Description of issue and why the EAG has identified it as important	According to NICE guidelines [NG115], all COPD patients should be offered the five fundamentals of care: smoking cessation; vaccinations (pneumococcal and influenza), pulmonary rehabilitation if indicated, co-development of a personalised self-management plan and optimised identification and treatment for comorbidities. ¹ Clinical advice and the submission from the patient organisation have however highlighted that access to COPD services and consistency of care across England is variable. ² Survey data (from 2025), reported in the patient organisation submission, highlighted that only 8.8% of their respondents received all five fundamentals of care. ^{2,3} Only 55% were offered smoking cessation, only 39% had a self-management plan and 32% were offered pulmonary rehabilitation (typically added to a long waiting list). Only 4.3% of COPD patients had completed a course of pulmonary rehabilitation. ^{2,4}
What alternative approach has the EAG suggested?	We believe this to be a currently unresolvable issue within the scope of this appraisal and a cause of considerable uncertainty. No alternative approaches are suggested.
What is the expected effect on the cost-effectiveness estimates?	If all COPD patients received the 'five fundamentals of COPD care' it is likely that patients would have reduced exacerbations (in terms of severity and frequency) and therefore deteriorate at a slower rate. As such, patients would have improved HRQoL, enabling them to work longer and delay treatment with mepolizumab. If patients already receive high-quality standard care, then the incremental benefit from mepolizumab would likely be smaller and would ultimately increase the ICER observed.
Could any additional evidence or analyses be provided to resolve this key issue?	Additional real-world evidence data could be collected to ascertain how inequalities in provision of the five fundamentals of COPD care affect mepolizumab efficacy.

Report Section	Text
Abbreviations: COPD = chronic obstructive pulmonary disease; HRQoL = health-related quality of life; ICER = Incremental cost-effectiveness ratio.	

Issue 2: Caregiver's burden has not been accounted for in the economic model

Report Section	Text
Description of issue and why the EAG has identified it as important	COPD imposes a substantial physical and psychological burden on patients and their families. Severe and persistent symptoms, particularly breathlessness, markedly reduce patients' quality of life and frequently necessitate informal caregiving by family members, who experience stress and unmet needs. ⁵ Patients commonly report feelings of dependency and guilt, perceiving themselves as a burden due to their reliance on others for everyday activities. ² NICE COPD guidelines [NG115] recommend the development of self-management plans inclusive of patients and caregivers or family members, these may include educational interventions and frequent reviews. ¹ Despite this, the Company states that caregiver costs were not considered in the economic model alluding to lack of cost data for England. ⁶
What alternative approach has the EAG suggested?	The EAG has not suggested any alternative approach to this issue as the Company has not collected the relevant data.
What is the expected effect on the cost-effectiveness estimates?	It is uncertain as these may depend on several variables such as the severity of the COPD, treatment adherence and caring resources available. The GOLD (Global Initiative for Chronic Obstructive Lung Disease) report 2025 estimates that direct medical expenditure for home-based care substantially underrepresents the true societal cost of COPD, as they fail to account for the significant economic value of unpaid care provided by family members. ⁷
Could any additional evidence or analyses be provided to resolve this key issue?	This important issue could be addressed by generating additional real-world evidence, such as prospective time-and-motion studies ⁸ or qualitative interviews and focus groups that quantify the time carers dedicate to supporting self-management, including administration of therapies such as mepolizumab, responding to exacerbations, attending healthcare appointments, and undertaking daily activities that patients with COPD are unable to perform independently. Applying an appropriate hourly cost to this time would enable estimation of the full economic burden of informal care and provide a more comprehensive assessment of total care costs.
Abbreviations: COPD = chronic obstructive pulmonary disease; EAG = External Assessment Group; GOLD = Global Initiative for Chronic Obstructive Lung Disease; QALY = quality-adjusted life year.	

Issue 3: Study selection biases in the clinical systematic literature review

Report Section	Text
Description of issue and why the EAG has identified it as important	The clinical systematic literature review (SLR) identified relevant evidence from five trials which were subsequently used to calculate indirect treatment effect estimates for mepolizumab versus dupilumab. An additional two studies conducted by the Company, IMPACT ⁹ and ECLIPSE, ¹⁰ were used to generate a pooled population to inform the baseline patient characteristics and impact of standard of care on HRQoL in the economic model. In the pooled analysis, 61% of patients from IMPACT were receiving dual therapy as opposed to triple therapy, representing 34% of the overall pooled population. Meanwhile ECLIPSE was conducted prior to the specified date range of the SLR and therefore was not identified in the SLR. Furthermore, ECLIPSE was an observational study making it ineligible according to the PICOS framework. Consideration of the potential introduction of study selection biases and inclusion of patients on dual therapy should be noted.
What alternative approach has the EAG suggested?	The EAG has not suggested any alternative approach to this issue.
What is the expected effect on the cost-effectiveness estimates?	It is uncertain whether other relevant evidence was missed in the searches or excluded due to the time frame or study design and therefore whether this may impact the expected cost effectiveness estimates. In addition, inclusion of patients on dual therapy may lead to underestimation of baseline utilities and disutilities.
Could any additional evidence or analyses be provided to resolve this key issue?	The Company could run sensitivity analyses to show the impact of not including data from IMPACT and ECLIPSE.
Abbreviations: EAG = External Assessment Group; HRQoL = health related quality of life; PICOS = population, intervention, comparison, outcome; SLR = systematic literature review	

Issue 4: Impact of COVID-19 affecting MATINEE and dupilumab trials

Report Section	Text
Description of issue and why the EAG has identified it as important	The indirect treatment comparison (ITC) incorporated five clinical trials. Three of these—one trial of mepolizumab (MATINEE) and two trials of dupilumab (NOTUS and BOREAS)—were conducted during the COVID-19 pandemic, whereas the remaining two mepolizumab trials (METREX and METREO) were conducted prior to the pandemic (see Table 3:15). Differences in trial timing may affect comparability of treatment effectiveness, as COPD exacerbation rates were substantially lower during the

Report Section	Text
	pandemic. ¹¹ This could make dupilumab appear less effective than mepolizumab, as the reduced number of exacerbations limits the ability of treatments to demonstrate an effect on exacerbation outcomes.
What alternative approach has the EAG suggested?	To address this issue, the EAG suggests that the Company conduct sensitivity analyses using only the 52-week follow-up data from the MATINEE, BOREAS and NOTUS trials, which were carried out during the COVID-19 pandemic.
What is the expected effect on the cost-effectiveness estimates?	Lower COPD exacerbation rates observed during the COVID-19 pandemic may have reduced the estimated cost-effectiveness of treatments. Applying non-pandemic exacerbation rates in the economic model would be expected to improve the estimated cost-effectiveness of dupilumab, however, the incremental cost-effectiveness of mepolizumab versus dupilumab would be expected to be lower.
Could any additional evidence or analyses be provided to resolve this key issue?	The Company could have applied treatment specific relative effects derived from pre- or post-pandemic data. Alternatively, this could be explored as a scenario, providing the data are available. Please see above “What alternative approach has the EAG suggested?”
Abbreviations: COPD = chronic obstructive pulmonary disease; EAG = External Assessment Group; ITC = indirect treatment comparison	

Issue 5: Unable to assess the proportional hazards assumption for the matching-adjusted indirect comparison (MAIC) comparing mepolizumab to dupilumab

Report Section	Text
Description of issue and why the EAG has identified it as important	The EAG requested evidence of the proportional hazards assumption being true (the hazard function is constant over time). The Company provided data showing proportional hazards was likely maintained between mepolizumab and placebo. This was accomplished via Kaplan-Meier curves, log-cumulative hazard plots and Schoenfeld residual plots (points for clarification (PfC) response, Question A3). ¹² However, no evidence was submitted for the assessment of the proportionality assumption between the mepolizumab and dupilumab, which are analysed using Cox proportional hazards in the MAIC for the secondary outcome of time-to-first moderate/severe exacerbation. If this assumption is not met sufficiently, the underlying assumption of the Cox analysis is threatened, a non-proportional hazards method may be preferred.

Report Section	Text
What alternative approach has the EAG suggested?	The EAG recommended using a non-proportional hazards method if this is violated. Additionally, if the assumption is not violated to conduct sensitivity analyses using Weibull, Gompertz, and exponential methods. The Company did provide the latter for mepolizumab compared to placebo.
What is the expected effect on the cost-effectiveness estimates?	This secondary outcome was not used in the economic modelling and therefore will not impact the results.
Could any additional evidence or analyses be provided to resolve this key issue?	The Company could provide evidence that the proportional hazards assumption also holds for the comparison mepolizumab versus dupilumab.
Abbreviations: EAG = External Assessment Group; MAIC = Matching Adjusted Indirect Comparison;	

Issue 6: The evidence from the pooled analysis included only a subset of patients from the METREX and METREO clinical trials

Report Section	Text
Description of issue and why the EAG has identified it as important	The pooled analyses to estimate the clinical effect estimates of mepolizumab only included a subset of participants from the METREX and METREO trials, who matched the characteristics of patients in the MATINEE trial. The selection of a patient subset undermines the randomisation process, meaning that the balance of prognostic factors may not be equally balanced between groups in the pooled analysis. It is also possible that the participants included in the pooled analysis were systematically different from those who were not included, and that selection was related to participant characteristics and outcomes. The EAG did not identify notable imbalances between the primary studies and the pooled analysis in relation to the baseline characteristics reported by the Company (CS Table 9). ⁶ However, this does not ensure comparability of participants in each of the trial arms in the pooled analysis. Given that the Company submitted the results from the pooled analysis as the core evidence supporting their submission, the EAG considers this to be a secondary issue.
What alternative approach has the EAG suggested?	The EAG has not suggested any alternative approach to this issue
What is the expected effect on the cost-effectiveness estimates?	The pooled analysis including only a subset of participants from the trials may introduce uncertainty in the treatment effectiveness modelled. It may also bias the incremental effectiveness estimates if the subset differs systematically

Report Section	Text
	from those who were not included. This may lead to under or over estimation of the ICER.
Could any additional evidence or analyses be provided to resolve this key issue?	The Company could run sensitivity analyses to show differences in efficacy between the restricted mITT-300 population and the broader populations included in the METREX and METREO trials.
Abbreviations: CS = company submission; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; mITT = modified intention-to-treat.	

Issue 7: Patients were excluded from the pivotal trials for mepolizumab if they presented with unstable or life-threatening cardiac disease or presented with other historic or current clinically significant comorbidities that were uncontrolled

Report Section	Text
Description of issue and why the EAG has identified it as important	Key comorbidities, such as diabetes or cardiac diseases, are common in real-world COPD populations. ¹³ However, in the three pivotal trials for mepolizumab (MATINEE, METREX and METRE), patients were excluded if they presented with unstable or life-threatening cardiac disease or presented with historic or current clinically significant neurological, psychiatric, renal, hepatic, immunological, endocrine or haematological abnormalities that were uncontrolled. ^{14,15} While clinically justified this limits the external validity of the evidence and introduces uncertainty regarding the generalisability of the observed treatment effects to the broader UK COPD population who are likely to receive mepolizumab in routine practice.
What alternative approach has the EAG suggested?	The EAG has not suggested any alternative approach to this issue.
What is the expected effect on the cost-effectiveness estimates?	Clinical advice to the EAG confirmed (if mepolizumab were recommended) that these patients would still be eligible for treatment in clinical practice and that there is a possibility that people with uncontrolled diabetes/cardiac disease may have worse outcomes. However, this would more likely be due to their co-morbidities and not due to their response to mepolizumab. The patients with comorbidities would incur additional management costs for the comorbidities and have worse quality of life compared to the population included in the trials. However, due to the lack of evidence in this population it is uncertain how this would affect the relative treatment effectiveness and the incremental cost. Therefore, the effect on overall incremental cost-

Report Section	Text
	effectiveness of mepolizumab for COPD treatment cannot be predicted.
Could any additional evidence or analyses be provided to resolve this key issue?	The collection of real-world data if mepolizumab is used in populations with uncontrolled or clinically significant comorbidities.
Abbreviations: CS = company submission; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio	

1.5 Company's modelling errors identified by the EAG

Modelling errors were identified and corrected by the EAG. Indirect costs for mepolizumab and dupilumab were calculated using an incorrect formula, with further details provided in EAG comments (see Section 4.2.9.2 and Section 6 - Appendix). Correction of this error increased the ICER reported in the Company's scenario (societal perspective), however the revised ICER remained close to the Company's base-case estimate and below the NICE willingness-to-pay threshold of £20,000 per QALY gain. The corrected ICER is presented as an EAG scenario analysis in Section 4.4.2. Nevertheless, as this societal perspective was exploratory, it does not affect decision making from the NHS and the personal social services (PSS) perspective.

In addition, the EAG considers early retirement percentages used in the Company models are not appropriate for a COPD cohort with starting mean age of 65.4 years and have resulted in incorrect calculations of indirect costs (see Section 4.2.9.2). Given that only a small minority of patients remain in paid employment at an age of 65.4 years and above, the use of more appropriate retirement percentages would only result in minimal costs associated with early retirement and productivity loss. Consequently, inclusion of indirect costs would have little impact on the ICER. Nevertheless, as stated in the paragraph above, the use of the Company's retirement percentages after correcting for the formula error did not result in any material difference in the Company's base-case ICER.

1.6 Summary of EAG's preferred assumptions and resulting ICER

Table 1:1 provides a summary of all the exploratory analysis that the EAG has undertaken in the updated Company base-case. The cost-effectiveness results of these exploratory analyses are presented in

Table 1:2 and

Table 1:3.

Deterministic results showed that the ICER for mepolizumab + standard of care (SoC) versus SoC was below the NICE cost-effectiveness threshold of £20,000/QALY. In addition, mepolizumab + SoC offered incremental net health benefits when compared against dupilumab + SoC.

Table 1:1: List of EAG exploratory analyses on Company base-case

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
1	For general population mortality, used national life tables for England and Wales (2018-2020) ¹⁶	Used national life tables for England and Wales (2022-2024) ¹⁷	A more recent life table to explore the potential impact of excess mortality from COVID-19 in recent years would help quantify the impact of these assumptions on the cost-effectiveness outcomes	4.2.7.1
2	Assume a relative risk mortality = 1 for people who discontinue the treatment versus	Assuming those who discontinue the treatment will have 10% higher risk of mortality	The characteristics of COPD patients who discontinue the treatment may differ from those	4.2.7.1

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
	those who do not		who respond to the treatment and remain on treatment. In the absence of evidence, it was therefore conservatively assumed that patients who discontinue have higher mortality risk	
3	The annualised discontinuation rate observed over the second year of the MATINEE trial (■■■■) was scaled to a per cycle probability of discontinuation (■■■■) and was used in the model for mepolizumab and dupilumab from Year 2 onwards. Alternatively, the lower bound (15%) of annual discontinuation (range of estimates from the real world between 15% to 25.8%) from the NICE dupilumab submission¹⁸ was explored as a scenario for mepolizumab and dupilumab for Year 2 onwards in the model	Upper bound (25.8%) of annual discontinuation for mepolizumab and dupilumab for Year 2 onwards in the model	Upper bound of discontinuation data was used to explore the impact of uncertainty	4.2.6

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
4	Error in the formula used to calculate the indirect costs in the Company's model trace sheets	Error in formula used to calculate the indirect costs corrected, but with the Company's retirement percentages, which the EAG finds inappropriately used	Use of corrected formula	4.2.9.2
Abbreviations: COVID-19 = Coronavirus disease 2019; EAG = External Assessment Group.				

Table 1:2: Deterministic results of EAG's exploratory analyses using Company's base-case model – mepolizumab + SoC versus SoC

Exploratory analysis number	Incremental costs (£)	Incremental QALYs	ICER £/QALY
Company base-case			£18,347
1			£18,185
2			£19,199
3			£18,984
4			£18,870
Abbreviations: EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; SoC = standard of care			

Table 1:3: Deterministic results of EAG's exploratory analyses using Company's base-case – mepolizumab + SoC versus dupilumab + SoC

Exploratory analysis number	Incremental costs (£)	Incremental QALYs	ICER £/QALY	Incremental NHB @WTP £30k
Company's base-case			Dominant	2.39
1			Dominant	2.41
2			Dominant	2.39
3			Dominant	1.37
4			Dominant	2.39
Abbreviations: EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; NHB= Net Health Benefit; QALY = quality-adjusted life year; SoC = standard of care; WTP = willingness-to-pay				

1.7 Outline of confidential comparator or subsequent treatment prices

The cost-effectiveness analysis presented in this report is based on patient access scheme (PAS) discounted for mepolizumab and list price for dupilumab. A confidential appendix, using the PAS discounted price for both dupilumab and mepolizumab to compare mepolizumab + SoC versus dupilumab + SoC, is included as part of the EAG report.

2 Background

This report critiques the Company Submission (CS) for mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237].⁶

Sections 2.1 and 2.2 include information and perspectives gathered from submissions by patient and professional organisations submitted to NICE: Asthma + Lung UK and Association of Respiratory Nurses (ARNS).^{2,19} In addition, the EAG also engaged with a clinical specialist in the topic area to inform the critique of these sections.

2.1 Critique of the Company's description of underlying health problem

This section provides a critique of the Company's description of COPD including the pathophysiology, epidemiology, diagnosis and classification, clinical presentation, and the burden of disease (covering HRQoL, caregiver burden and treatment-related burden; CS Section 1.3.1).⁶

Table 2:1: Summary of the EAG critique of the Company's description of the condition

Area of health condition addressed	Section in the CS were reported	EAG comment
Pathophysiology	CS, Section 1.3 ⁶	Appropriate Aligns with published literature
Epidemiology	CS, Section 1.4.1 ⁶	Appropriate

Area of health condition addressed	Section in the CS were reported	EAG comment
		Aligns with published literature and comparator submission.
Natural history	Not Reported in CS	Not reported No dedicated Section on the natural history of COPD was included in the CS. The Company has alluded to the natural history in a reference (Ref 15) ²⁰ and in the health economics Section (CS, p. 142). ⁶
Diagnosis and classification	CS, Section 1.3.1.3 ⁶	Appropriate Aligns with published guidelines (GOLD and NICE) ^{1,7}
Clinical presentation	CS, Section 1.4.3.1 ⁶	Appropriate Aligns with published literature
Burden of disease (covering health-related quality of life, caregiver burden and treatment-related burden)	CS, Section 1.4.3.2 ⁶	Some concerns Aligns with published literature but not applied in clinical studies.
Abbreviations: COPD = chronic obstructive pulmonary disease; CS = company submission; EAG = External Assessment Group; GOLD = Global Initiative for Chronic Obstructive Lung Disease		

2.1.1 Burden of disease

Disease burden including clinical, quality of life and economic burden is included in CS Section 1.4.3.⁶ The Company report that the population likely to receive mepolizumab experience systemic inflammation due to elevated blood eosinophil levels that contribute to a high burden of symptoms and comorbid conditions. Comorbidities are substantially more prevalent in people with COPD than in those without (86.0% vs. 48.9% in a UK primary care study)²¹ and are associated with an increased risk of mortality. Exacerbations are also common and are a major cause of hospitalisation, mortality, and cardiovascular events, with risks highest shortly after an exacerbation and increasing cumulatively with recurrent events, particularly following severe or hospitalised episodes. The Company's interpretation of disease burden in the population likely to receive mepolizumab aligns with the GOLD 2025 guidelines for high eosinophilic COPD patients, and is reflective of the current UK population.^{7,21}

The EAG notes that while the Company's description of disease burden is consistent with GOLD 2025 guidance and reflects the high symptom, comorbidity, and

exacerbation burden observed in UK clinical practice, the population studied in the clinical trials included in this appraisal was more narrowly defined. For example while key comorbidities, such as diabetes or cardiac diseases, are common in real-world COPD populations, patients were excluded if they presented with unstable or life-threatening cardiac disease or presented with historic or current clinically significant neurological, psychiatric, renal, hepatic, immunological, endocrine or haematological abnormalities that were uncontrolled,^{14,15} resulting in a highly selected trial cohort. This limits the external validity of the evidence and introduces uncertainty regarding the generalisability of the observed treatment effects to the broader UK COPD population who are likely to receive mepolizumab in routine practice (see Secondary Issue 7).

Citing research from COPD voices,²² the Company describes caregiving in COPD as imposing a substantial emotional, physical, social, and financial burden, particularly during exacerbations. Caregivers often feel unprepared and experience anxiety, fatigue, social isolation, and negative impacts on work, relationships, and personal time, with the burden especially marked among older caregivers with comorbidities. In their research, the Company reports that caregivers may spend up to 50 hours per week providing care to people with COPD.²²

We note an inconsistency between the Company's recognition of substantial caregiver burden and its exclusion of caregiver costs from the economic model. Given the reported intensity of informal care and its potential implications for productivity loss, health service use, and quality of life, omission of these costs is likely to underestimate the true societal impact of COPD and the potential value of interventions that reduce exacerbations. While the Company cites a lack of England-specific data,⁶ this limitation should be explicitly acknowledged as a source of uncertainty, and the implications of excluding caregiver costs should be explored through scenario or sensitivity analyses. The EAG has made this a secondary issue (Secondary Issue 2) for this submission.

2.1.1.1 HRQoL

Quality of life is covered in detail in the CS (Section 1.4.3.2). The Company focused on aspects that impact wellbeing such as symptoms (Section 1.4.3.2.1), exacerbations (Section 1.4.3.2.2), anxiety and depression (Section 1.4.3.2.3), physical limitations (Section 1.4.3.2.4) and the impact on caregivers (Section 1.4.3.2.5).⁶

The Company notes that COPD patients likely to receive mepolizumab (GOLD E category) have greater physical limitations than those at other stages of COPD (GOLD A and B categories) and that impacts on caregivers' burden is often under-recognised.⁷ A large Spanish cohort study identified substantial caregiver burden among informal caregivers of people with COPD, with high proportions reporting health, social, and work-related problems. Caregiver burden increased significantly with patient dependence, with caregivers of highly dependent patients having markedly higher risks of health, professional, and leisure-related difficulties.²³ In line with recent literature recommendations,⁵ the Company suggests that caregiver burden should be considered when evaluating interventions to prevent exacerbations. Despite this, the Company declares that 'whilst caregiver burden has also been documented, caregiver costs were not considered in the model due to the lack of available cost data in England' (CS, Section 3.5.4, p. 173).⁶

2.1.1.2 Treatment burden

Treatment burden is presented in CS Section 1.4.4.1.⁶ Professional contributions to this appraisal noted that the goals of COPD management are symptom reduction, improved exercise tolerance, and better health status. In parallel, treatment aims to reduce risk by preventing disease progression, preventing and treating exacerbations, and reducing mortality. Professional contributions from the ARNS established that a clinically meaningful treatment response in COPD includes improvements in symptoms and exercise tolerance, measurable gains in lung function, reductions in exacerbations, hospitalisations and mortality, and better patient-reported quality of life and daily functioning.¹⁹

The CS cites the five “fundamentals of care” for COPD included in the NICE guidelines¹ but notes the low and inconsistent uptake across England. This is in line with patients’ experience of non-pharmacological interventions for COPD.²

“I would like to complete a course in pulmonary rehabilitation, as I believe it would help me to manage my symptoms. However, I know in my area there are long waiting lists.” – person responding to survey from Asthma + Lung UK submission.²

Pharmacological treatment is amply covered in Section 1.4.4.1.2, citing NICE relevant guidelines and recommendations in addition to the GOLD 2025 guidelines.^{1,7} The Company remark on the existing unmet need for patients who continue to exacerbate despite triple inhaled therapy, and explain that there are no targeted biologic therapies routinely available within the NHS as dupilumab (an IL-4/IL-13 inhibitor) is currently under NICE appraisal as an add-on maintenance treatment for uncontrolled COPD in adults with raised blood eosinophils, with final guidance imminent.²⁴

Data provided to this submission by Asthma + Lung UK found that current COPD therapies do not adequately meet patient needs, with many individuals continuing to experience recurrent exacerbations and progressive lung function decline despite treatment.² Evidence from UK patient surveys highlights substantial unmet need and poor access to fundamental COPD care, including smoking cessation support, pulmonary rehabilitation and self-management plans, leaving many patients insufficiently supported to manage their condition.³ Furthermore, patient insights inform of the adverse effects of current treatment options and their lack of confidence in the effectiveness of the treatment.² The addition of new treatments was highlighted to give patients hope that they will be able to gain better control of their symptoms and improve their quality of life.²

It was also raised that there is an unmet need to help reduce administration of high-dose steroid inhalers,² however this aspect of current treatment is not addressed in this technology appraisal (see Section 2.2.2 for more details). Easier administration through monthly injections were also highlighted by patients as potential benefits of new biologic therapies such as mepolizumab.²

2.2 Critique of the Company's overview of current service provision

This section provides a critique of the Company's description of current service provision in the UK (CS Sections 1.4 and 1.5), treatment guidelines (CS Section 1.4.4.1), unmet need (CS Section 1.4.5), and proposed position of mepolizumab in the treatment pathway (CS Section 1.4.6).⁶ Equality considerations are covered in CS Section 1.5 and will also be considered in this section.⁶

Table 2:2: Summary of the EAG critique of the Company's overview of current service provision

Area of current service provision addressed	Section of the CS where reported	EAG comment
Targeted therapies	CS, Sections 1.4.4.1.4 and 1.4.5 ⁶	Appropriate Currently there are no targeted therapies for uncontrolled eosinophilic COPD approved for use in the NHS but a number of drugs are already in the NICE assessment process (dupilumab ²⁵ and mepolizumab). Other treatments, for example itepekimab, are currently being reviewed by NICE [NICE ID6547], ²⁶ and others are in trials due to complete in the next 12 months or more (for example, tezepelumab (NCT05507242), ²⁷ solrikritug (NCT06496620), ²⁸ and tozorakimab (NCT06897748) ²⁹).
Treatment guidelines	CS, Section 1.4.4.1 ⁶	Secondary Issue 1 The Company cite the NICE NG115 ¹ COPD guidelines and the international GOLD 2025 report (which was the most recent version at the time of the Company's submission). ³⁰ The GOLD report has recently undergone a major revision: the GOLD 2026 report. ³⁰ Clinical advice to the EAG and professional and patient organisation submissions mentioned the low percentage of the eligible COPD population that receive the NICE [NG115]

Area of current service provision addressed	Section of the CS where reported	EAG comment
		guidelines recommended five fundamentals of COPD care at diagnosis and on an ongoing basis as well as other aspects of care.^{1,2,19} Please see Section 1.4 (Secondary Issue 1) and Section 2.2.1 for more details. See also Section 2.2.4 (Equality considerations).
Unmet need	CS, Section 1.4.5 ⁶	Some concerns The Company highlight that there are currently no NICE approved targeted biological therapies for uncontrolled eosinophilic COPD available in the NHS and state that availability would widen the treatment options for people with this uncontrolled condition. Please see Section 2.2.2 for more details. The patient organisation's 2025 survey highlights the very low percentage (8.8%) of people with COPD receiving the five fundamentals of treatment as outlined in the NICE [NG115] COPD guidelines.^{1,2} Please see Secondary Issue 1.
Company's proposed position of the intervention in the treatment pathway	CS, Section 1.4.6 ⁶	Some concerns Clinical advice to the EAG was that this proposed positioning of the intervention in the treatment pathway was appropriate. The patient and professional submissions raise a number of potential logistical and other issues related to the current treatment pathway and any proposed changes.^{2,19} Please see Section 2.2.3 for more details.
Equality considerations	CS, Section 1.5 ⁶	Some concerns The NICE scope³¹ did not raise any equality issues however concerns about equality were raised in the CS as well as by patient and professional submissions and clinical advice to the EAG.^{2,19} These related to a number of protected characteristics including age,

Area of current service provision addressed	Section of the CS where reported	EAG comment
		disability, sex, socioeconomic factors, factors affecting access to care and not worsening disparities. Please see Section 2.2.4 for more details.
Abbreviations: COPD = chronic obstructive pulmonary disease; CS = company submission; EAG = External Assessment Group; GOLD = Global Initiative for Chronic Obstructive Lung Disease		

2.2.1 Treatment guidelines

Treatment guidelines are covered in CS, Section 1.4.4.1.⁶ Current NICE guidelines [NG115] state that those with 1 severe or 2 moderate COPD exacerbations within a year should receive a long-acting beta-agonist (LABA) + a long-acting muscarinic antagonist (LAMA) + inhaled corticosteroids (ICS)^{a, 1}. The guidelines also state that this should be additional to the five fundamentals of COPD care: smoking cessation; vaccinations (pneumococcal and influenza), pulmonary rehabilitation if indicated; co-development of a personalised self-management plan and optimised identification and treatment for comorbidities.¹ These fundamentals should be revisited at every review along with continued demonstration of satisfactory inhaler technique (optimising inhaler technique). The guidelines go on to state that if the person is still limited by breathlessness or subject to frequent exacerbations further treatment options should be explored with a healthcare professional (see Secondary Issue 1, Section 1.4).¹

The Company cite the NICE NG115¹ guidelines as well as the international GOLD 2025 report.³⁰ Clinical advice to the EAG is that the international GOLD report is used in the NHS. The EAG note that, subsequent to the CS, the GOLD 2025 report has undergone major revisions, and the GOLD 2026 report is now available.³⁰

The main change found in the GOLD 2026 report is “The criteria defining GOLD A, B and E categories have been adjusted due to emerging evidence from observational studies that even one moderate or severe exacerbation prior to initiating maintenance pharmacological therapy increases the risk of subsequent events... The

^a The NICE guidelines warn of the increased risk of side effects in people who take ICS and state that the reason for continuing ICS treatment should be documented in clinical records.

threshold of one moderate exacerbation should now be used to consider treatment escalation, with the aim of achieving a low disease activity state characterized by no exacerbations” (p. iv).³⁰ Clinical advice to the EAG has indicated that this change in the GOLD 2026 report would make no difference to the Company’s proposed position of the intervention in the treatment pathway.

Other changes in the GOLD 2026 report (Figure 3.11 and p. 66), include an option for the use of biologic therapy, for patients on triple therapy who still have exacerbations and a blood eosinophil count (BEC) of ≥ 300 cells/ μ L “consider adding dupilumab (if chronic bronchitis (CB)) or mepolizumab (with and without CB)” (p. 66).³⁰ The GOLD 2026 report also updates their guidance on vaccination that local guidelines should be followed and that vaccines for COVID-19, influenza, pneumococcal and respiratory syncytial virus (RSV) have been shown to decrease the incidence of respiratory tract infections. Their immunisation committees recommend routine use of shingles vaccine as well as DTaP vaccination (tetanus, diphtheria and pertussis) for those who have not previously received this vaccination in adolescence.³⁰

The Company also refer to NICE TA461 (guidance for use of roflumilast)³² and NICE ID6235 GID-TA11246 (guidance in development for use of dupilumab).²⁵ The professional organisation submission from ARNS also mentioned use of NICE quality standard QS10 in England which is mainly based upon NICE NG115.^{1,19}

2.2.2 Unmet need

Unmet need is covered in CS, Section 1.4.5.⁶ There are currently no NICE approved targeted biological therapies for uncontrolled eosinophilic COPD available in the NHS and the Company state that availability would widen the treatment options for people with this uncontrolled condition. The patient organisation also flag a large unmet need, for people with COPD who report to them that they feel “trapped in a vicious cycle of exacerbations and lung function decline” (response 8, p. 6).² These patients hope that biological therapies would help end this cycle.

The patient and professional submissions to this assessment process as well as clinical advice to the EAG all highlight the variability and inconsistency of optimised care across England.^{2,19} The patients' association says that "Only when basic care needs are met, and care is optimised, can the rest of the unmet needs be met by the introduction of mepolizumab".² The organisation goes on to state that currently only a very low percentage (8.8% as reported in Asthma and Lung UK's 2025 survey)² of people with COPD receive the five fundamentals of COPD treatment as outlined in the NICE [NG115] guidelines (see Section 2.2.1 for more details).¹ For example, in their 2025 survey only approximately 55% of respondents with COPD were offered treatment and support for smoking cessation, 63% were offered pulmonary rehabilitation, 44% were offered optimisation of treatment for comorbidities and 84% were offered an influenza vaccination.³ These fundamentals should be revisited at every review along with continued demonstration of satisfactory inhaler technique.¹ ARNS also suggest promoting an active lifestyle and patient education to help self-management and "Breathlessness management and airway clearance strategies".¹⁹

In the patient organisation submission one respondent to the Health Unlocked Forum survey questioned how effective their current treatments were "I hardly use my bronchodilator inhaler as it doesn't seem to do anything" (response 7, p.6).² There is no information as to whether the respondent had access to treatment review and a healthcare professional to discuss other treatment options as recommended in the NICE guidelines.¹

ARNS recommend that other care is optimised first before prescribing of mepolizumab is considered: this would mean making sure that the five fundamentals recommended in the NICE guidelines including lifestyle/behavioural interventions and SoC as already exists in the NICE guidelines are optimised before prescribing of a biologic therapy is considered.¹⁹ They also recommend that there is improvement in risk stratification for exacerbations and proactive management by developing and implementing "improved tools to identify and support 'rising risk' patients, enabling earlier and targeted interventions" (response 8, p.3).¹⁹ Additionally they recommend enhanced patient support and education to "empower patients in self-management, symptom monitoring, and adherence to treatment plans" (response 8, p.3).¹⁹

According to the patient organisation submission some people with COPD would like to be able to taper their ICS dose to reduce their adverse effects but have been told that this is not currently an option and are hoping that the introduction of biological therapies may help reduce their ICS use.² The GOLD 2026 report notes that if “blood eosinophils are ≥ 300 cells/ μ L [ICS] de-escalation is more likely to be associated with the development of exacerbations” (p.66 and Figure 3.9, GOLD 2026 report).³⁰ In response to clarification question A8 the Company responded that tapering of ICS was not studied in the three included studies (MATINEE, METREX and METREO).¹² Clinical advice to the EAG stated there is no expectation that there would be any change in inhaled steroid dose when mepolizumab is used in this population.

2.2.3 Positioning of mepolizumab in the care pathway

The Company’s proposed position of mepolizumab in the treatment pathway is as an add-on maintenance treatment for adult patients with uncontrolled COPD (defined as ≥ 2 moderate or ≥ 1 severe exacerbations within 12 months) of an eosinophilic phenotype (defined as BEC ≥ 300 cells/ μ L) on a combination of an ICS, a LABA, and a LAMA (CS Section 1.4.6).⁶ Clinical advice to the EAG is that this proposed positioning of the intervention in the treatment pathway was appropriate.

However the professional submission (ARNS) suggests, for appropriate prescribing of mepolizumab and ongoing follow up and care for those receiving it to take place, an integrated care pathway linking primary and secondary care or specialist community respiratory hubs would be needed.¹⁹ Current care is self-administered but as mepolizumab is administered subcutaneously on a four weekly basis assisted administration would potentially be needed for some patients. Proper identification of a moderate or severe exacerbation would be important for prescription of mepolizumab to be appropriate and to avoid overprescribing. ARNS also recommend that training and education of healthcare professionals would need to be provided to achieve these aims. They suggest the potential involvement of a multidisciplinary team to assess suitability for treatment.¹⁹ ARNS recommend that

other care is optimised first before prescribing of mepolizumab is considered (see Section 2.2.1 for more details of the five fundamentals of COPD care).¹⁹

The patient organisation raises the issue of how best to administer the biological therapy and report that for some people with COPD having to travel outside the home to receive an injection on a four weekly basis may be very difficult due to the financial cost of travel.² The organisation hopes that “a sufficiently designed, inclusive patient pathway would negate this concern, and key lessons on patient accessibility, such as home administration, should be learnt from the severe asthma biologics pathway and the Accelerated Access Consensus pathway for uncontrolled and severe asthma” (response 10, p.9).² They say “Home administration of biologics for severe asthma patients has worked well, reducing geographical barriers to access. COPD patients are generally older; therefore, it will be important to consider that some may have dexterity limitations and struggle to self-administer injections at home” (response 13, p.11).²

Asthma and Lung UK note the importance of knowing how mepolizumab will interact with comorbidities – as nearly 80% of people with COPD have at least one or more comorbidities.² However, as discussed in Section 2.1.1, the EAG note there were stringent exclusion criteria applied to comorbidities in the pivotal mepolizumab trials; patients were excluded if they presented with unstable or life-threatening cardiac disease or presented with historic or current clinically significant neurological, psychiatric, renal, hepatic, immunological, endocrine or haematological abnormalities that were uncontrolled,^{14,15} The EAG considers this to be secondary issue (Secondary Issue 7).

2.2.4 Equality considerations

Equality considerations are covered in CS Section 1.5.⁶ NICE did not note any equality issues in the decision problem,³¹ however concerns about equality were raised in the CS as well as by patient and professional submissions and clinical advice to the EAG.^{2,19} These related to a number of protected characteristics under the Equality Act 2010 including socioeconomic factors, factors affecting access to care and not worsening disparities.³³

The CS highlights a number of important issues related to higher prevalence and more frequent exacerbations in lower socioeconomic groups as well as higher levels of co-morbidity in people with COPD and unequal access across England to optimised COPD care, such as access to smoking cessation support and pulmonary rehabilitation if appropriate, as recommended by the NICE NG115 guidelines.¹

2.2.4.1 Socioeconomic factors

Socioeconomic deprivation is an important factor in terms of initial (later) diagnosis, higher prevalence of COPD, ongoing access to care and far higher rates of hospital admissions for exacerbations in winter (compared to the least deprived).³⁴ Based on their report on COPD in the UK Asthma and Lung UK state that a person “... from the poorest 10% of households is more than two and a half times more likely to have COPD than someone from the most affluent 10% of households” (response 12, p.10).^{2,35} Both the Company and Asthma and Lung UK cite an Asthma and Lung UK report that “Poorer people with COPD have more exacerbations, and the poorest people with COPD are being left further behind in terms of the care that they are receiving” (response 12, p.10).^{2,36} Further exacerbations can lead to a further decline in health as found by a Canadian study that both the Company and clinical advice to the EAG highlighted “The risk of the subsequent severe exacerbation was increased threefold after the second severe exacerbation and 24-fold after the 10th, relative to the first” (p. 957).²⁰

2.2.4.2 Unequal access to care and factors affecting access to care

The professional organisation submission (ARNS) states that people with exacerbations have variable and unequal access to care and services as regards both availability and consistency across England whether they are in primary or secondary care – this applies to availability of optimisation of their care pre-discharge (during hospitalisation for an exacerbation) and post-discharge review and timely follow up to ensure they are receiving guideline-based treatment recommended for those post-exacerbation.¹⁹ NICE Quality Standard (QS 10) recommends that “People discharged from hospital after an acute exacerbation of chronic obstructive pulmonary disease (COPD) receive a hospital discharge care

bundle.” This discharge care bundle includes the five fundamentals of COPD care but as flagged by the professional and patient organisations as well as clinical advice to the EAG is not equally available across England.^{2,19,37} The professional organisation (ARNS) mentioned variable access to spirometry for initial diagnosis of COPD¹⁹ and also importantly access to spirometry for ongoing monitoring of COPD.³⁸

The Association of Respiratory Nurses (ARNS) highlights that mepolizumab administration may exacerbate health inequalities.¹⁹ As a four-weekly subcutaneous treatment, access may be limited for some people with COPD due to travel, mobility, carer support, cost, or rurality, and additional services may be required for those unable to self-administer.¹⁹

Digital exclusion can be a problem for some (including: older people; rural areas; lack of digital literacy) even though availability of digital tools for COPD self-management may help access for others.⁶

2.3 Critique of the Company's definition of decision problem

This Section provides a critique of the Company's interpretation of the decision problem (CS Section 1.1).⁶

Table 2:3: Summary of the decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with uncontrolled COPD with raised blood eosinophils (eosinophilic phenotype).	Adult patients with uncontrolled COPD (defined as ≥ 2 moderate or ≥ 1 severe exacerbations within 12 months) of an eosinophilic phenotype (BEC ≥ 300 cells/ μ L) on a combination of an ICS, a LABA, and a LAMA.	The NICE final scope covers all adults with uncontrolled COPD with raised blood eosinophils. The anticipated licence [REDACTED] [REDACTED] This appraisal applies the MATINEE trial criteria: • Uncontrolled COPD (≥ 2 moderate or ≥ 1 severe exacerbation[s] in the prior year) despite triple therapy, and • Blood eosinophils ≥ 300 cells/μL at screening and ≥ 150 cells/μL in the prior year.	Some concerns The NICE final scope covers all adults with uncontrolled COPD and raised blood eosinophils, while the Company defines a narrower population based on moderate or severe exacerbations, eosinophils ≥ 300 cells/μL, and use of triple inhaled therapy.³¹ Although the Company defines severity by exacerbation history rather than GOLD staging, the supporting trials included patients across GOLD stages 2–4. GOLD 2026 guidance supports escalation to LABA+LAMA with added ICS for patients with BEC ≥ 300 cells/μL, indicating this threshold predicts greatest treatment benefit.³⁰ The EAG therefore recognises that there has been a narrowing of scope, and this is further explored in Section 2.3.1.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			The BEC ≥ 300 cells/μL threshold is recognised in COPD reports (e.g. GOLD 2025⁷) as a reliable biomarker of treatment responsiveness, and biologic trials have shown greater and more clinically meaningful reductions in exacerbations in this subgroup.^{14,22,25,39-41} Evidence is drawn from the overall MATINEE mITT population and the pooled mITT-300 population (MATINEE mITT plus the BEC ≥ 300 cells/μL at screening subgroups from METREX and METREO).	
Intervention	Mepolizumab as an add-on to maintenance treatment.	In line with NICE scope.	NA.	Appropriate The EAG agree that the mepolizumab as an add-on to maintenance treatment is in line with the NICE scope.³¹ The EAG also highlight the importance of the five fundamentals of COPD care which should be revisited at every review,¹ and acknowledge there are important inequalities in provision (see Secondary Issue 1, Section 1.4).
Comparator(s)	Standard care without mepolizumab Dupilumab with double or triple therapy (subject to NICE evaluation).	Standard care without mepolizumab (triple inhaled therapy).	Patients with COPD who continue to experience exacerbations despite optimised inhaled therapy are typically managed with triple therapy (ICS/LABA/LAMA). There are currently no routinely available long-term treatment options beyond	Some concerns The NICE scope includes standard care and dupilumab as comparators,³¹ with dupilumab under NICE evaluation and expected to be published in February 2026.²⁵ The Company initially used an ITC to assess relative efficacy of mepolizumab

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			inhaled therapies. Roflumilast (TA461) and azithromycin may be considered only in selected cases but are not in scope for this appraisal.^{1,32} Roflumilast (TA461)³² is rarely used in UK clinical practice due to poor tolerability and safety concerns (real-world data indicate ~5% patients receive it (46)), and azithromycin used in infection-driven COPD, is limited by safety and monitoring requirements.¹ Dupilumab (an IL-4/IL-13 inhibitor) is currently undergoing NICE appraisal as an add-on maintenance treatment for uncontrolled COPD with an eosinophilic phenotype, with final guidance imminent at the time of this submission. It therefore represents the most relevant emerging comparator for mepolizumab. While dupilumab is not yet established as routine SoC, comparison with optimised inhaled therapy remains important; however, dupilumab use is expected to increase over time, making cost-comparison vs. dupilumab a valid scenario.	compared with dupilumab, but the EAG requested a multilevel network meta-regression (ML-NMR), which was completed for the primary outcome of frequency of moderate or severe exacerbations.¹² Having received clinical advice, the EAG concurs that there are no routinely used treatments beyond inhaled therapies and the fundamentals of COPD care (see Secondary Issue 1, Section 1.4). Further discussion of the EAG's comments related to the list of comparators is provided in Section 2.3.2.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Outcomes	Lung function Frequency of moderate or severe exacerbations Frequency of exacerbations resulting in hospital admission or ED visit Symptom control Mortality Adverse effects of treatment HRQoL.	Outcomes are available in line with NICE scope.	All outcomes specified in the scope have been provided. However, the therapeutic value of biologic therapies in COPD lies in reducing exacerbations, which are clinically important events that significantly impair QoL, drive hospitalisations, and contribute to long-term disease progression (Section 1.4.3 ⁶).^{7,22,40} Exacerbation reduction is therefore a key treatment goal in eosinophilic COPD,⁴¹ reflecting both the clinical burden of the disease and the priorities of patients and clinicians. Severe exacerbations are a major driver of disease progression, mortality, and healthcare burden: a single severe event increases the risk of a subsequent exacerbation by 64% and the risk of death by 21%,⁴² with recurrent exacerbations compounding this risk further (15, 47). Among patients hospitalised for a severe COPD exacerbation, approximately 4–5% die during admission, and a further 9–11% die within 30 days of discharge, according to national data from the OHID. Around one-third (30–35%) of patients are readmitted or die within 90 days of discharge, reflecting	Some concerns The outcomes reported in MATINEE/METREX and METREO match those reported in the scope.³¹ The primary endpoint in all three clinical trials was annualised rate of moderate/severe exacerbations. The submission uses an ITC and MAIC to assess effectiveness and only five outcomes were presented for the Bucher ITC/MAIC (and directly used in the cost-effectiveness modelling). Furthermore only the primary outcome (annualised rate of moderate/severe exacerbations was included in the ML-NMR.¹² This narrowing of outcomes (which the EAG agreed was a pragmatic decision at the PfC meeting), whilst understandable, is of some concern and is detailed in Section 2.3.3.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			the ongoing vulnerability of this population. ⁴³ These events also place a substantial burden on healthcare systems, accounting for up to 45% of total direct COPD costs. ⁴⁴	
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment	In line with NICE scope.	The core submission presents a CEA of mepolizumab vs. SoC, supported by evidence from MATINEE and the pooled mITT-300 analysis showing clinically meaningful reductions in exacerbations. However, as dupilumab is currently undergoing NICE appraisal (ACM2, 5 August 2025) for the maintenance treatment of uncontrolled COPD with raised blood eosinophils and final guidance release is imminent, the CEA also includes dupilumab as a comparator (focusing on the annualised rate of moderate/severe exacerbations). In addition, GSK believes a CC against dupilumab is relevant, given that the MAIC showed no statistically significant differences in exacerbation or HRQoL outcomes between treatments, indicating at least similar of greater health benefit. Notably, mepolizumab demonstrated numerically better efficacy compared with dupilumab for key exacerbation outcomes, including	Appropriate In line with the NICE reference case.³¹

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.		severe exacerbations in patients with investigator-defined CB. Accordingly, both CEA and CC scenarios are presented within this submission. The MAIC necessarily excluded several subgroups of patients enrolled in the mepolizumab programme (e.g. without CB, GOLD 4 disease, or BEC <300 cells/μL) that were not eligible for the dupilumab trials, however for these patients, benefit was demonstrated for mepolizumab vs. placebo and these data are used to inform the comparison of mepolizumab vs. SoC in the CEA.	
Subgroups	If the evidence allows, the following subgroups of people may be considered: • Levels of eosinophils (at least 500 cells per microlitre) • Severity of COPD • Frequency of exacerbation within previous 12 months • CB or not • Smoking status.	Subgroup data are available in line with NICE scope.	Data for subgroups specified in the scope have been provided in Section 2.8.⁶	Appropriate All subgroups identified in the NICE scope³¹ were pre-specified in the key trials (MATINEE, METREX and METREO). Due to the small sample sizes of many of these subgroups, which reduce the power of the analyses, caution is warranted in interpreting the results.
Special considerations	NA.	Higher disease burden: COPD	While the NICE scope does not specify any equality or equity	Some concerns

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
including issues related to equity or equality		disproportionately affects individuals from socioeconomically disadvantaged backgrounds compared with those from more advantaged groups. Greater comorbidity load: These populations are more likely to have multiple co-existing health conditions, which can complicate management. Increased exacerbation risk: Disadvantaged patients are at higher risk of frequent exacerbations and hospitalisations compared with those from less disadvantaged backgrounds.	considerations, it is well established that COPD disproportionately affects individuals from socioeconomically disadvantaged backgrounds who also tend to have a higher comorbidity burden and consequently, are at higher risk of experiencing exacerbations and hospitalisations. ^{36,45} Given this, the potential for a well-tolerated and effective treatment to reduce exacerbations in this group is particularly important and relevant to NICE's commitment to reducing health inequalities. Including these considerations helps to ensure that the impact on underserved populations is appropriately reflected in this appraisal. Some patients may face barriers to attending healthcare appointments, including psychosocial and practical challenges. ⁴⁶ The potential to reduce these, through less frequent dosing, acknowledges and accommodates patterns of healthcare avoidance.	The EAG agree that socioeconomic deprivation increases the risk of developing COPD, and people in deprived areas often develop COPD earlier, experience more severe symptoms and exacerbations, and face barriers to accessing healthcare and effective treatments. As a result, deprivation is linked to worse clinical outcomes, higher hospitalisation rates, and increased mortality in COPD patients. The impact of inequalities was not explored in the economic model. Equity issues are discussed further in Section 2.2.4 (and are not repeated here).

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Source: CS, Section 1.1, Table 1⁶ Abbreviations: ACM = Appraisal Committee Meeting; BEC = blood eosinophil count; CC = cost comparison; CEA = cost-effectiveness analysis; COPD = chronic obstructive pulmonary disease; CS = company submission; EAG = External Assessment Group; ED = emergency department; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HRQoL = health-related quality of life; ICS = inhaled corticosteroid; IL-4 = interleukin-4; IL-13 = interleukin-13; ITC = Indirect Treatment Comparison; LABA = long-acting beta2-agonist; LAMA = long-acting muscarinic antagonist; MAIC = matching-adjusted indirect comparison; mITT = modified intention-to-treat; µL = microlitre; ML-NMR = multi-level network meta-regression; NA = not applicable; OHID = Office for Health Improvement and Disparities; PSS = Personal Social Services; QALY = quality-adjusted life year; QoL = quality of life; SoC = standard of care; TA = technology appraisal.				

2.3.1 Population

The NICE final scope covers all adults with uncontrolled COPD with raised blood eosinophils,³¹ whereas the Company defines the population of interest in the CS as adult patients with uncontrolled COPD (defined as ≥ 2 moderate or ≥ 1 severe exacerbations within 12 months) of an eosinophilic phenotype (BEC ≥ 300 cells/ μ L) on a combination of an ICS, a LABA, and a LAMA. The Company state the anticipated licence [REDACTED] (p. 18).⁶

Importantly, the Company approach defines severity on exacerbations and not the GOLD staging for COPD which classifies COPD severity based on post-bronchodilator FEV1 (forced expiratory volume in one second) (% predicted, see

Table 2:4). Interestingly however, the eligibility criteria for the included trials in this submission (MATINEE, METRIX and METREO) include COPD severity in their inclusion criteria (GOLD stages 2 to 4) in accordance with the definition by the ATS/ERS^b (also reported in Table 2:4)⁴⁷ as well as exacerbation history. This differs in comparison to the proposed scope by the Company (which focuses solely on exacerbations).

^b ATS = American Thoracic Society; ERS: European Respiratory Society

Table 2:4: COPD Staging

	Spirometric classification by Celli et al. 2004		GOLD staging*		
COPD Severity	Postbronchodilator FEV1/FVC	FEV1 % pred	GOLD Stage	FEV1/FVC Ratio	FEV1 (% predicted)
At risk**	>0.7	≥80			
Mild	≤0.7	≥80	I	<0.70	≥80
Moderate	≤0.7	50-80	II	<0.70	50%-79
Severe	≤0.7	30-50	III	<0.70	30%-49
Very severe	≤0.7	< 30	IV	<0.70	<30
Source: Table 1 Spirometric classification by Celli et al. 2023 ⁴⁷ (left); Figure 2.10 ³⁰ (right) Abbreviations: COPD = chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; GOLD = Global initiative for chronic Obstructive Lung Disease; pred = predicted. Footnotes: *Based on post-bronchodilator FEV1; ** Patients who smoke or have exposure to pollutants, have cough, sputum or dyspnoea.					

Until recently, there was no agreed-upon definition of a COPD exacerbation or its severity.⁴⁸ For the past 20 years, severity has mostly been classified retrospectively based on healthcare use and treatments given, useful for clinical trials but not for real-time clinical care. GOLD 2026 now proposes defining exacerbation severity (mild, moderate or severe) based on the clinical characteristics of the patient (according to the ROME proposal).^{7,49}

Eligibility for the trial reflected NICE [NG115] recommendations for triple therapy (LAMA + LABA + ICS),¹ including patients with a history of frequent (≥2 moderate) and/or severe (≥1) exacerbations in the preceding year. For patients with one or more moderate or severe exacerbation(s) in the previous year (Group E), the GOLD 2026 guidelines recommend LABA+LAMA (plus ICS if eosinophil counts are ≥ 300 cells/μL).³⁰ This is broadly consistent with the decision problem (aside from referencing one or more exacerbations of moderate or severe intensity) addressed by the Company which references an eosinophil count of ≥ 300 cells/μL.⁶ The GOLD 2026 guidelines state that a threshold of a blood eosinophil count ≥ 300 cells/μL identifies the ‘top of the continuous relationship between eosinophils and ICS, and can be used to identify patients with the greatest likelihood of treatment benefit with ICS’ (p. 150).³⁰ As such, this eosinophil threshold seems appropriate and matches up

with the Company's requirement of inhaled combination therapy. Older NICE guidance (last reviewed January 2022) details when inhaled combination therapy (ICS + LAMA + LABA) is appropriate within UK clinical practice:¹

- When patients have spirometrically confirmed COPD and do not have asthmatic features/features suggesting steroid responsiveness and remain breathless or have exacerbations despite (i) having used or been offered treatment for tobacco dependence if they smoke and, (ii) optimised non-pharmacological management and relevant vaccinations and, (iii) using a short-acting bronchodilator.
- When patients with COPD who are taking LABA+ICS and when their day-to-day symptoms continue to adversely impact their quality of life or they have a severe exacerbation (requiring hospitalisation) or they have two moderate exacerbations within a year.
- When patients with COPD who are taking a LAMA + LABA if they have a severe exacerbation (requiring hospitalisation) or they have two moderate exacerbations within a year.
- When patients with COPD who are taking LAMA+LABA and whose day-to-day symptoms adversely impact their quality of life (inhaled combination therapy should be trialled for three months and followed by a clinical review).

According to clinical advice received by the EAG, practice varies, but blood eosinophil counts are commonly used to guide ICS initiation, with low counts discouraging and high counts supporting the decision to start ICS.

2.3.2 Comparators

The NICE scope lists two comparators; (i) standard care without mepolizumab and, (ii) dupilumab with double or triple therapy (subject to NICE evaluation). Guidance for dupilumab for maintenance treatment of controlled COPD with

raised BEC was in development with NICE (ID6235) at the time of submission by the Company, and has an expected publication date of 11 February 2026.²⁵ In the CS, whilst dupilumab was noted as currently undergoing NICE appraisal, it was recognised that its use (if it was to be given approval) will likely increase over time (p. 19).⁶ As such, the Company presented a cost-comparison between mepolizumab and dupilumab which is appropriate when a new health technology is likely to deliver similar or greater health benefits than an existing (recommended) intervention. The Company originally provided indirect efficacy estimates of comparative efficacy between mepolizumab/dupilumab derived from a MAIC. The EAG's preferred approach was a ML-NMR,⁵⁰ which has been used in previous NICE technology appraisals,⁵¹ and was requested in the PfC (question A2). In their response,¹² the Company did perform an ML-NMR. Given time constraints, the Company presented analysis only for the primary outcome, number of moderate or severe exacerbations which the EAG recognises is a key outcome driving the economic modelling (further discussion of the ML-NMR is presented in Section 3.5).

The Company also outlined in the decision problem that there are no routinely available treatment options currently in use beyond inhaled therapies (p. 18).⁶ Roflumilast (TA461)³² and azithromycin are rarely used due to poor tolerability and safety concerns, and this was confirmed by clinical advice to the EAG. NICE guidance details five treatments and plans which should be considered 'fundamentals of COPD care' (NG115).¹ These include (i) treatment and support to stop smoking; (ii) pneumococcal and influenza vaccinations; (iii) pulmonary rehabilitation (if indicated); (iv) a personalised self-management plan; and (v) the optimisation of treatments for comorbidities.¹ Smoking cessation in particular has been shown to be particularly beneficial for active smokers. A recent meta-analysis has shown that smoking cessation offered significant benefits to COPD patients, notably in the improvement of specific key indicators of pulmonary function (FEV1% predicted, FEV1/FVC), alleviating symptoms, enhancing exercise tolerance, and potentially reducing mortality.⁵² Clinical advice to the EAG indicates that access to pulmonary

rehabilitation and smoking cessation services may not be uniformly available to all patients with COPD. However, with respect to pharmacological management, all relevant and appropriate comparator treatments have been included in this appraisal.

One additional treatment is currently in the NICE appraisal process; itepekimab as add-on maintenance treatment for moderate to severe chronic obstructive pulmonary disease [ID6547].²⁶ Therefore, there is the possibility an additional comparator which may receive NICE guidance in the medium term.

2.3.3 Outcomes

The NICE scope includes outcomes related to lung function, frequency of moderate or severe exacerbations, frequency of exacerbations resulting in hospital admission or ED visit, symptom control, mortality and adverse events (AEs) of treatment.³¹ The Company states all outcomes specified in the scope have been included, however it is important to highlight that this reporting refers only to the MATINEE/METRO/METREX trials and therefore mepolizumab compared with standard of care treatment. Frequency of moderate/severe exacerbations is expressed as the annualised rate of moderate/severe exacerbations in the trial evidence, which the EAG considers appropriate.

The submission also uses an ITC to assess effectiveness of mepolizumab compared to dupilumab, in which five outcomes were considered:^{6c}

- Annualised rate of moderate/severe exacerbations
- Annualised rate of severe exacerbations

^c These five outcomes were estimated using two different definitions of CB using investigator assessment and based on SGRQ-C responses at baseline (see Table 35).⁶

- Time to first moderate/severe exacerbation
- Change from baseline for St George's Respiratory Questionnaire for COPD (SGRQ-C) total score at week 52
- SGRQ-C total score responses at week 52

Indirect treatment effects of mepolizumab versus dupilumab were calculated for the outcomes listed above. In response to PfC (question A2), the Company also conducted an ML-NMR with annualised rate of moderate or severe exacerbations as the sole outcome.¹² The EAG considers exacerbations to have a significant and prolonged impact on health status and outcomes, and negative effects on pulmonary function⁵³ and is satisfied that exacerbations represent the most important outcome driving economic modelling (annualised rate of moderate/severe exacerbations and annualised rate of severe exacerbations are included in the Company base-case). The EAG discussed this approach with the Company in the PfC meeting, and agreed that for the reasons outlined above, this was the most important outcome and given the tight time frame for responses, was a pragmatic solution to enable comparison between mepolizumab and dupilumab.

The EAG is satisfied therefore that the most important outcomes used for cost-comparison modelling are available for the comparator technology (mepolizumab versus dupilumab) and other outcomes included in the NICE scope are included in the Company trials only.

3 Clinical effectiveness

This section presents a summary and critique of the clinical-effectiveness evidence included in the CS. Section 3.1 provides a critique of the Company's systematic review of clinical and safety evidence. Sections 3.2 and 3.3 provide a critique of the included studies and clinical-effectiveness analyses.

Section 3.5 provides a critique of the indirect treatment comparison and Section 3.7 provides the conclusions of the clinical effectiveness Section.

3.1 Critique of the methods of the review

The Company conducted a SLR to identify clinical evidence on patients with moderate, severe, or very severe COPD receiving treatment with ICS-based triple therapy (ICS+LABA+LAMA) with or without an add-on therapy or dual therapy (LABA+LAMA) with add-on therapies.⁵⁴ The methods for the Company’s SLR of clinical evidence are detailed in the CS, Appendix B.⁵⁴ The original SLR was conducted in October 2016 (covering 2013 to October 2016), and subsequently updated in August 2018, June 2024 and August 2025. The Company stated that the SLR was conducted in accordance with the Centre for Reviews and Dissemination (CRD) guidance⁵⁵ and that it complied with the NICE Process and Methods Guide (PMG36).⁵⁶ The Company also state that they conducted the review “in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards” (p.8),⁵⁷ however the PRISMA standards are ‘reporting standards’ rather than ‘conduct standards’. A summary of the EAG’s critique is presented in Table 3.1 below.

Table 3:1: Summary of the EAG's critique of the methods implemented by the Company to conduct the SLR

Systematic review stage	Section in the CS where methods are reported	EAG’s assessment of the robustness of the methods
Data sources	Appendix B, Section B.1.1 ⁵⁴	Appropriate An appropriate range of bibliographic databases were used. Additionally, grey literature was searched together with an appropriate range of conference proceedings and clinical trials registries.
Search strategies	Appendix B, Section B.1.1.7, p.g12-88 ⁵⁴	Appropriate Given the very broad nature of the search, the EAG concludes that subject headings and keywords were appropriate and captures all relevant conditions. The use of broad severity and

Systematic review stage	Section in the CS where methods are reported	EAG's assessment of the robustness of the methods
		staging terms and the reliance on an unreviewed 2016 strategy introduce some uncertainty around precision and coverage of newer terminology. Updating the strategy to reflect current indexing could improve relevance and robustness.
Search filters	Appendix B, Section B.1.1.7, pp. 12-88 ⁵⁴	Some concerns The EAG has identified that either a modified or outdated CDA (formerly CADTH) filter was used. See Section 3.1.2 for further information.
Eligibility criteria	Appendix B, Section B.1.2.1.2 ⁵⁴	Some concerns The original eligibility criteria applied for the 2016 SLR and 2018 update were expanded for the 2024 SLR update that required rescreening of records excluded from the 2016 and 2018 reviews. The EAG note that the eligibility criteria were broader than the NICE scope, ³¹ and are not aware of a publicly available protocol. See Section 3.1.3 for further information.
Study selection	Appendix B, Section B.1.2.2 ⁵⁴	Secondary Issue 3 The clinical SLR identified five trials which met the inclusion criteria and which were subsequently used to calculate indirect treatment effect estimates for mepolizumab versus dupilumab. However two studies which either: did not meet the eligibility criteria (IMPACT) ⁹ or were not identified by SLR (ECLIPSE) ¹⁰ were used to generate a pooled population to inform the baseline patient characteristics and impact of standard of care on HRQoL in the economic model (see Section 1.4, Secondary Issue 3 and Section 3.1.4 for further information).

Systematic review stage	Section in the CS where methods are reported	EAG's assessment of the robustness of the methods
Data extraction	Appendix B, Section B.1.3 ⁵⁴	Appropriate Data were extracted by a single reviewer and then checked independently by a second reviewer. This meets the minimum acceptable standard. ⁵⁵ New subgroups were added for the 2024 SLR update and data for these were extracted.
Quality appraisal	Appendix B, Section B.1.4 ⁵⁴	Appropriate The Company state that risk of bias (RoB) assessment was based on the methods in the Cochrane Handbook (version 6.5, August 2024 update). ⁵⁸ This would mean use of the RoB2 tool however the Company added two further domains needed for Australian submissions. Cochrane do not recommend adding additional domains. ⁵⁹ There is no explicit statement that two or more reviewers undertook independent RoB assessment. This would meet minimum acceptable standards and therefore the EAG consider this approach acceptable.
Evidence review	CS, Section 2.2 ⁶	Secondary Issue 3 The SLR identified relevant evidence from five trials that aligned to the NICE scope ³¹ and were subsequently used to calculate indirect treatment effect estimates for mepolizumab versus dupilumab. An additional two studies by the Company, were used to generate a pooled population to inform the economic model, which may introduce selection bias and underestimate the baseline utilities and disutilities. See Section 3.1.5 for further information.
Abbreviations: CADTH = Canadian Agency for Drugs and Technologies in Health, now known as Canada's Drug Agency, CDA); CS = company submission; EAG = External Assessment Group; HRQoL = health-related quality of life; RoB = risk of bias; SLR = systematic literature review		

3.1.1 Search strategies

Searches were conducted separately for clinical effectiveness, and for economics (which is critiqued separately in Section 4.1.1). An appropriate range of electronic databases were searched, and the Company report the use of pre-tested study design filters.⁵⁴ Searches were appraised by the EAG using the Peer Review of Electronic Search Strategies (PRESS) checklist.⁶⁰

No restrictions were placed on geography, publication date or language, but conference proceedings were limited to the year of the search (2025) and were subject to the same eligibility criteria as full text publications.⁵⁴ Searches were originally conducted in October 2016, with the final updated search in August 2025, so they can be considered up to date.

3.1.2 Search filters

The Company has referenced the use of the CADTH (Canadian Agency for Drugs and Technologies in Health, CADTH, now known as Canada's Drug Agency, CDA) filter for randomised controlled trials and SIGN and stated that they were modified to fit the needs of the review. However, it is not recommended to modify a pre-tested filter. In Appendix B.1.2.10.2, Table 19⁵⁴ the study design lists randomised controlled trials but has not explicitly stated the exclusion of quasi-experimental trials. Therefore, the amendment of the CADTH filter to remove quasi-experimental trials may lead to potentially relevant trials and publications being missing.

The use of the DC (date created) and DD (first date) field in the updates of the Embase and ED (entry date) and DT (create date) in the Medline search, created some minor concerns. It is important to assess whether this field is the most appropriate choice compared to alternatives (e.g., year of publication), as the behaviour of DC or DD is dependent on current indexing practices. If applied inappropriately, this could lead to either increased noise or the exclusion of relevant records.

3.1.3 Eligibility criteria

The eligibility criteria for the SLR changed over time. The original population and intervention eligibility criteria applied for the original 2016 SLR and the 2018 update were expanded for the 2024 SLR update.

The original population included “patients with chronic obstructive pulmonary disease (COPD) who had at least one exacerbation in the previous year” (Section B.1.2.1.1, p. 81) whereas the 2024 and 2025 SLR updates included “adult patients (≥ 18 years) with a diagnosis of moderate to very severe COPD” (Section B.1.2.1.1, p. 81).⁵⁴ The criteria presented are broader than the NICE population criteria in that they are not limited to ‘uncontrolled’ COPD or by eosinophil level. Other population-related inclusion criteria also changed for the 2024 SLR update (for example, earlier versions of the review excluded those with a diagnosis of COPD for less than one year and a history of one or more exacerbations in the previous 12 months). It is unclear which SLR eligibility criteria are presented in Table 19 (Section B.1.2.1.2); the Company state that the criteria were ‘pre-specified’ but the Company do not state when exactly this pre-specification took place - for instance the Company seem to present the updated 2024 update SLR population criteria but show a mixture of 2018 population subgroups of interest and some new subgroups. The EAG are therefore uncertain as to the full original eligibility criteria for the 2016 review and it is also uncertain as to what question(s) the original 2016 SLR and 2018 SLR update were answering and what the original searches were meant to retrieve. This uncertainty makes it difficult to properly critique the search methods and strategies. A protocol for the original 2016/2018 SLR or 2024/2015 SLR update has not been provided by the Company and there is no mention of the protocol being publicly available. The provision of the protocol(s) and a section in the SLR report detailing deviations from original protocol would have been helpful and improved transparency of reporting.

The interventions covered by the SLR also appear to have changed for the 2024 SLR update - the original review included only studies where participants were “receiving an ICS as part of the triple-based (with or without

add-ons) regimen” (Section B.1.2.1.1, p. 82).⁶¹ For the 2024 SLR update this was expanded to include participants receiving “dual inhaled maintenance therapy (LABA and LAMA) plus an add-on” (Section B.1.2.1.1, Table 19, p. 83).⁶¹

The Company only included publications from 2013 onwards but give no reason for this limitation (and yet the Company include individual patient data (IPD) from the ECLIPSE observational study published in 2008 in the pooled analysis which was used to inform the economic model, see Section 3.1.3 for more details). Limiting to inclusion of English language publications only could lead to bias and potentially informative results being missed.

3.1.4 Study selection

Study selection was covered in CS Appendix B, Section B.1.2.2.⁵⁴ Five trials met the eligibility criteria and were included in the SLR of clinical effectiveness. However the Company also included an additional two studies that did not meet the eligibility criteria, IMPACT⁹ and ECLIPSE,¹⁰ which were used to inform the economic model. IMPACT was retrieved by the clinical searches for the clinical effectiveness SLR but approximately two thirds of participants were receiving dual therapy and so did not meet the eligibility criteria. ECLIPSE was not picked up by the SLR as it was published in 2008 before the cut-off date for the searches (2013), and it did not meet the study design criteria in that it was an observational study rather than a randomised controlled trial (RCT). Consideration of the potential introduction of study selection biases and inclusion of patients on dual therapy should be noted and the EAG have raised this as a secondary issue (please see Secondary Issue 3 in Section 1.4 for more details).

The Company state that title and abstract screening were undertaken by two independent reviewers but although two reviewers undertook full text screening the Company did not explicitly state that this was undertaken independently (Section B.1.2.2). This does not meet best practice standards but does meet the minimum acceptable level of rigour.⁵⁵

The changes to the eligibility criteria for the 2024 SLR update necessitated the rescreening of 2,555 records that were excluded from the original 2016 SLR and the 2018 update. It is unclear from the PRISMA diagrams for 2016 and 2018 which 2,555 records these were. In the 2016 original SLR there were 6,665 records excluded at title and abstract screening stage (and 69 at the full-text screening stage) and for the 2018 update SLR 1,220 records had been excluded at title and abstract screening (with 19 records excluded at full-text stage) (Figure 1, Appendix B).⁵⁴ The Company report that 13 additional studies were included because of this rescreening process. The EAG are broadly satisfied that the relevant eligible studies have been identified and included.

3.1.5 Evidence review

In total the original 2016 SLR and subsequent updates (2018, 2024, 2025) included 120 publications reporting on 65 RCTs. From these 65, only 3 RCTs (MATINEE, METREX, METREO) were identified investigating mepolizumab added to ICS-based triple therapy, in patients with moderate-to-very severe COPD in line with the decision problem.^{6,54} A fourth study, COPD-HELP (NCT04075331),⁶² investigating mepolizumab treatment post-hospitalisation in patients with COPD with an eosinophilic phenotype was also identified and provided as supportive information in the CS. Clinical effectiveness evidence relevant to the comparator dupilumab (added to ICS-based triple therapy), under the NICE appraisal process at the time of the CS, was identified in two RCTs; both Phase 3 RCTs (BOREAS and NOTUS) in patients with moderate-to-severe COPD.⁶³

The EAG acknowledge the five trials MATINEE, METREX, METREO, BOREAS and NOTUS offer the most relevant available evidence on the treatment effects of mepolizumab and comparator dupilumab in line with the NICE scope.³¹ Subsequently in the CS they have been used to estimate treatment effects which later on inform the Company's de novo economic model (see Section 3.2 and 3.3 and 3.4 for further details). The COPD-HELP trial included in the CS as supportive evidence, indicated that patients with

more severe and progressed COPD, do not experience a significant difference in the primary endpoint of time to all-cause rehospitalisation or death with mepolizumab treatment compared to placebo and the authors argued mepolizumab be positioned earlier in the treatment pathway for this patient population.⁶² Moreover, in this UK, single-centre based study, mepolizumab treatment was demonstrated to significantly reduce moderate or severe exacerbations in this patient population (RR 0.81; 95% CI 0.66, 1.00), albeit not severe exacerbations alone.^{62,64}

An additional two studies IMPACT and ECLIPSE were used to generate a pooled population to inform the baseline patient characteristics and impact of standard of care on HRQoL in the economic model (see Sections 4.2.3 and 4.2.8). While only data from patients eligible for the MATINEE trial were included in the pooled population (patients with ≥ 2 moderate or ≥ 1 severe exacerbations in the prior year and BEC ≥ 300 cells/ μ L), the EAG notes some biases and limitations in the evidence selected. The ECLIPSE study,¹⁰ included in the CS due to the availability of IPD was published prior to the specified date range of the SLR and was therefore not identified in the literature searches. Moreover, ECLIPSE was a 3-year longitudinal study to identify clinically relevant COPD subtypes as well as characteristics and biomarkers of disease progression. As an observational study it does not meet the inclusion criteria specified in the PICOS framework. While the EAG note baseline patient characteristics presented in the CS (Table 37 CS Appendix J)⁶⁴ appear to closely match that of the the mITT-300 population of the mepolizumab studies (MATINEE, METREX and METREO), there are concerns regarding selection bias and whether other existing evidence was missed in the searches or excluded due to the time frame or study design.

IMPACT, included in the clinical effectiveness SLR was a multi-centre double blind RCT comparing triple therapy with dual therapy in patients with COPD.⁹ The EAG highlight that while included in the SLR, IMPACT provides the only subset of patients receiving dual therapy in the pooled analysis, as opposed to triple therapy. This presents 61% of patients included from IMPACT

(1,018/1,676) in the pooled analysis and 34% of patients overall in the pooled analysis (Table 37 CS Appendix J).⁶⁴ The EAG agree the remaining baseline patient characteristics presented in the CS for the subset of patients included from IMPACT reflect that of the mITT-300 population of the mepolizumab studies. However, IMPACT showed that, compared with triple therapy, dual therapy resulted in a significantly smaller mean improvement in SGRQ total score and a lower proportion of patients achieving an SGRQ response (≥ 4 -point reduction), with both outcomes significant at $P < 0.001$.⁹ EQ-5D-5L data collected in IMPACT was used to inform the Company's base-case, while scenario analysis was conducted using SGRQ scores from IMPACT and ECLIPSE. Therefore, baseline utilities and disutilities calculated may be underestimated due to inclusion of patients on dual therapy.

Overall, the EAG approves the inclusion of data from IMPACT and ECLIPSE into the pooled analyses to increase the analytical power, however, consideration of the potential introduction of study selection biases and inclusion of patients on dual therapy should be noted (see Section 4.2.8 for further details).

3.2 Critique of the methods of the trials for the technology of interest

The main source of clinical effectiveness evidence on mepolizumab as an add-on treatment to triple inhaled therapy (ICS + LABA + LAMA) in patients with COPD with elevated blood eosinophils comes from three international, multi-centre, randomised, double-blind, placebo-controlled phase 3 trials: MATINEE (NCT04133909), METREX (NCT02105948) and METREO (NCT02105961).⁶⁵⁻⁶⁷

In MATINEE, patients with COPD characterised by type 2 inflammation, defined by elevated blood eosinophils ($\text{BEC} \geq 300 \text{ cells}/\mu\text{L}$ at screening and $\geq 150 \text{ cell } \mu\text{L}$ within the previous 12 months) and a history of ≥ 2 moderate or ≥ 1 severe exacerbation(s) in the prior year were enrolled.^{6,65} A total of 804 patients were randomised 1:1 to receive either 100mg mepolizumab ($n = 403$)

or placebo (n=401) subcutaneously (SC) every four weeks alongside triple inhaled therapy for 52 weeks and up to 104 weeks.⁶ MATINEE was conducted at 361 locations in 25 countries including the UK, Belgium, Denmark, France, Germany, Greece, Ireland, Italy, the Netherlands, Spain, Sweden, Hungary, Poland, Canada, USA, Argentina, Brazil, Mexico, China, Republic of South Korea, Taiwan, Australia, India, Israel and New Zealand.^{6,65} Patients were recruited from October 2019 through August 2023. Recruitment was halted between March 23 and June 9, 2020, because of the Covid-19 pandemic.¹⁴

METREO enrolled COPD patients with a BEC of ≥ 150 cells/ μ L at screening or ≥ 300 cells/ μ L within the past 12 months prior to screening. A total of n= 674 participants, who covered a broad clinical spectrum including CB or emphysema and GOLD stage 2–4 disease, were randomised in a 1:1:1 ratio to receive mepolizumab 100mg SC (n= 223), mepolizumab 300mg SC (n= 225) or placebo (n = 226) every four weeks for 52 weeks alongside triple inhaled therapy.⁶⁴ METREO was conducted between 24 April 2014 and 16 January 2017 in 168 sites across 15 countries (UK, US, Argentina, Australia, Canada, Chile, Denmark, Germany, Japan, Republic of Korea, the Netherlands, Romania, Slovakia, Taiwan and Ukraine).^{64,67}

Lastly, the METREX trial was conducted between 15 April 2014 and 17 January 2017⁶⁶ in 117 investigative sites, across 16 countries not including the UK (Australia, Belgium, Canada, Czech Republic, Estonia, France, Greece, Italy, Mexico, Norway, Peru, Poland, Russian Federation, Spain, Sweden, US).⁶⁴ A total of 836 participants, who covered a broad clinical spectrum including CB or emphysema and GOLD stage 2–4 disease, were randomised 1:1 to receive mepolizumab 100mg SC (n= 417) or placebo (n = 419) every four weeks for 52 weeks alongside triple inhaled therapy.⁶⁴

An overview of the EAG's critique of these trials is presented in Tables 3.2 - 3.6, below.

Table 3:2: Summary of EAG's critique of the MATINEE, METREO, METREX and mITT-300 pooled analysis methods

Trial design or conduct concept	MATINEE	METREO	METREX	mITT- 300 Pooled analysis
Eligibility criteria	Secondary Issue 7	Secondary Issue 7	Secondary Issue 7	Secondary Issue 7
Subgroups	Appropriate	Appropriate	Appropriate	Appropriate
Intervention	Appropriate	Appropriate	Appropriate	Appropriate
Comparator	Appropriate	Appropriate	Appropriate	Appropriate
Randomisation	Appropriate	Appropriate	Appropriate	Secondary Issue 6
Allocation concealment	Appropriate	Appropriate	Appropriate	NA
Blinding	Appropriate	Appropriate	Appropriate	NA
Statistical analyses	Appropriate	Appropriate	Appropriate	Secondary Issue 6
Outcomes	Appropriate	Appropriate	Appropriate	Appropriate
Abbreviations: mITT-300 = modified intention-to-treat 300 (participants with BEC $\geq$ 300 cells/ μ L at screening who received $\geq$ 1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline); NA = Not applicable.				

Table 3:3: Summary of MATINEE methods critique

Trial design or conduct concept	Section in the CS where methods are reported	EAG's assessment
Eligibility criteria	CS, Section 2.3.1.1, Table 6, p. 57-58	Secondary Issue 7 MATINEE enrolled adults aged ≥ 40 years who were current or former smokers (≥ 10 pack-years) with moderate-to-very-severe COPD (GOLD 2–4), eosinophilic inflammation (BEC ≥ 300 cells/μL at screening or ≥ 150 cells/μL in the prior 12 months), impaired lung function, a recent history of frequent or severe exacerbations, and receiving optimised ICS-based triple background therapy. The EAG is concerned that the MATINEE trial population is narrower than the population defined in the NICE scope.³¹ The EAG also notes that people with certain comorbidities were excluded from the clinical trials, which affects the representativeness of participants to UK clinical practice. See Section 3.2.1 and Section 1.4 for further details.
Subgroups	CS, Section 2.3.1.1, Table 6, pp. 60-61 and Table 11, p. 75.⁶ Sciurba et al, 2025, p. 1717 and Supplemental Appendix, Figure S5.¹⁴	Appropriate The EAG considers the subgroups evaluated in MATINEE to be appropriate, as they were pre-specified, reflect prognostic factors for COPD and are aligned to the NICE scope.
Intervention	Sciurba et al. 2025, Supplementary Appendix, p.12¹⁴ PfC response letter¹² MEA114092⁶⁸ MEA112997⁶⁹	Appropriate In MATINEE patients were randomised 1:1 to receive 100mg mepolizumab (SC injection) or placebo every 4 weeks. Injections were administered for at least 52 weeks and up to a maximum of 104 weeks, in addition to ICS-based triple inhaled therapy (i.e., ICS plus two additional COPD medications; ≥ 12 months maintenance dose ICS and ≥ 3 months on fluticasone propionate ≥ 500 g/day or equivalent + LABA + LAMA).

Trial design or conduct concept	Section in the CS where methods are reported	EAG's assessment
		The 100mg SC regimen was considered the target effective dose based on results from Studies MEA114092⁶⁸ and MEA112997⁶⁹, in patients with asthma, which was further supported by the METREO trial in patients with COPD.¹⁵ Furthermore, the SoC in MATINEE is aligned to the NICE scope and proposed Marketing Authorisation,^{31,70} which confirm that ICS-based triple inhaled therapy in MATINEE corresponds to UK clinical practice. The EAG is satisfied with the intervention used in MATINEE trial.
Comparator	CS, Section 2.2, Table 5, p. 52 ⁶	Appropriate Participants in the control group received placebo (SC injection of 0.9% sodium chloride) every 4 weeks in addition to SoC defined as ICS-based triple inhaled therapy for 52 or 104 weeks. The EAG is satisfied that the comparator was appropriate and aligns with the NICE scope.⁶
Randomisation	Sciurba et al, 2025, Supplementary appendix, p. 19 ¹⁴	Appropriate The randomisation schedule was generated by PPD (ThermoFisher Scientific, USA) using validated randomisation SAS Software Version 9.4 (Proc Plan). Patients were centrally randomised using an Interactive Web Response System (IWRS) with a fixed block size of 4. Randomisation schedules were shuffled and stated to be created for each country using validated software. Overall, the EAG is satisfied that the randomisation was performed adequately, and this is supported by the balance in baseline characteristics between treatment groups.
Allocation concealment	Sciurba et al, 2025, Supplementary appendix, p.19 ¹⁴	Appropriate As stated above a IWRS was used for randomisation with a fixed block size of 4. A fixed block size can introduce bias; however, schedules were shuffled to prevent sequential ordering

Trial design or conduct concept	Section in the CS where methods are reported	EAG's assessment
		or grouping of treatment and kit and thus unblinding. The EAG therefore considers methods for allocation concealment appropriate.
Blinding	Sciurba et al, 2025, Supplementary appendix, p. 19 ¹⁴	Appropriate MATINEE was a double blinded trial, investigators, participants and trial sponsors were blinded during treatment assignment and evaluation. Mepolizumab and placebo were administered to participants by investigators, both blinded to treatment allocation, using the same route, volume and dosing schedule. In case of an emergency unblinding was allowed by the investigator; this is ethically necessary to protect participant safety, while restricting it to investigator judgment helps preserve blinding integrity. Treatment discontinuation was required after unblinding, but patients were permitted to continue in the study, with reason for unblinding formally documented to ensure transparency and regulatory compliance, minimising bias in outcome assessment. Although the blinding of outcome assessors are not explicitly specified in the protocol, clinical and safety outcomes were evaluated by blinded investigators, making blinded outcome assessment likely. The EAG is therefore satisfied with this approach to blinding.
Statistical analyses	CS, Section 2.4.1, Table 11, pp. 73-4 ⁶	Appropriate MATINEE was 90% powered to detect a statistically significant reduction in the annualised rate of moderate/severe exacerbations. The trial used a hierarchical step-down testing strategy to compare mepolizumab versus placebo (PBO) in the mITT population, controlling multiplicity at a two-sided 5% alpha level, with secondary endpoints tested sequentially only if earlier endpoints were significant, while non-

Trial design or conduct concept	Section in the CS where methods are reported	EAG's assessment
		hierarchical results were considered nominal (exploratory) due to lack of multiplicity control. The Company define the mITT population as all randomised patients who received at least one dose of trial medication. For efficacy endpoints, patients were analysed by randomised treatment. For safety, patients were analysed based on actual treatment received for more than 50% of treatment administrations. The trial was powered to detect a true 23% reduction in the annualised rate of moderate/severe exacerbations with mepolizumab. The EAG finds the statistical analyses and power calculations appropriate.
Outcomes	CS, Section 2.3.1.1, Table 6, p. 60 and Table 21, pp.85-86 ⁶ MATINEE CSR p. 5 ⁷¹	Appropriate The outcomes reported in MATINEE align with the NICE-specified outcomes, covering exacerbation frequency and severity, exacerbations requiring hospitalisation or emergency care, symptom control, HRQoL, mortality, lung function and treatment safety. HRQoL and symptom control were assessed using disease-specific clinically validated, instruments, including the COPD Assessment Test (CAT), St George's Respiratory Questionnaire (SGRQ), and the Evaluating Respiratory Symptoms in COPD (E-RS:COPD).⁷²⁻⁷⁴
Abbreviations: BEC = Blood eosinophil count; CAT = COPD Assessment Test; CS = company submission; COPD = Chronic Obstructive Pulmonary Disease; CSR = Clinical Study Report; EAG = External assessment group; E-RS:COPD = Evaluating Respiratory Symptoms in COPD; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HRQoL = Health-Related Quality of Life; ICS = Inhaled Corticosteroid; IWRS = Interactive Web Response System; LABA = Long-Acting Beta₂-Agonist; LAMA = Long-Acting Muscarinic Antagonist; mg = Milligram; mITT = Modified Intent-to-Treat; PBO = Placebo; PfC =points for clarification; SC = Subcutaneous; SoC = Standard of Care; µL = Microlitre.		

Table 3:4: Summary of METREO methods critique

Trial design or conduct concept	Section in the CS where methods are reported	EAG's assessment
Eligibility criteria	Appendix J, Section J.2.1, Table 8, p. 13. ⁶⁴	Secondary Issue 7 METREO included patients aged ≥40 years, with moderate-to-very severe COPD (GOLD 2–4), type 2 inflammation (BEC ≥150 cells/μL at screening or ≥300 cells/μL in prior 12 months), a history of ≥2 moderate or ≥1 severe exacerbation in the 12 months before screening and use of ICS (fluticasone propionate ≥500 μg or equivalent), LABA, and LAMA for ≥3 months immediately prior to screening. Patients with a current diagnosis of asthma, non-smokers with a history of asthma, those with unstable COPD and those with clinically significant abnormalities or disease were excluded. The EAG has some concerns that the population of the METREO trial is narrower than the population included in the NICE scope.³¹ The EAG also notes that people with certain comorbidities were excluded from the clinical trials, which affects the representativeness of participants to UK clinical practice. See Section 3.2.1 and Section 1.4 for further details.
Subgroups	Appendix J, Section J.2.4, table 11, p. 19. ⁶⁴	Appropriate Pre-specified subgroup analyses for the primary outcome were: -All patients who received at least one dose of study treatment -Patients who received at least one dose of study treatment and with blood eosinophil counts ≥ 150cells/uL at screening or ≥300 cells/uL in the 12 months prior The EAG considers the pre-specified subgroups in the METREO trial to be appropriate and in line with the NICE scope.
Intervention	Appendix J, Section J.2.1. table 8, p.14. ⁶⁴ METREO CSR, p. 31 ⁷⁵	Appropriate Participants were allocated to receive mepolizumab either 100mg or 300mg via SC injection every 4 weeks, in addition to SoC (triple inhaled therapy), for 52 weeks. However, the CS focuses on the 100mg dose based on previous studies in patients with

Trial design or conduct concept	Section in the CS where methods are reported	EAG's assessment
		asthma (MEA112997 and MEA114092) reporting the effect on absolute bioavailability of SC mepolizumab and the dose response established on blood eosinophil count to be effective. ⁷⁵ The EAG is satisfied that the intervention is aligned to the NICE scope and proposed Marketing Authorisation. ^{31,70}
Comparator	Appendix J, Section J.2.1. table 8, p. 14. ⁶⁴	Appropriate Participants in the PBO group received placebo (SC injection) every 4 weeks for 52 weeks and SoC (triple inhaled therapy) reflective of UK practice as confirmed by clinical advisors to the EAG. The comparator listed in the NICE scope is standard care without mepolizumab. The EAG is satisfied that placebo in addition to standard of care (triple inhaled therapy) is an appropriate comparator.
Randomisation	METREO CSR Section 4.5.2, pp. 35-36.⁷⁵ Pavord 2017 (Supplementary appendix)¹⁵	Appropriate Following screening, patients were randomised 1:1:1 ratio to receive 100mg mepolizumab, 300mg mepolizumab or PBO. Randomisation was performed by using a centralised, computer generated (using [REDACTED]), permuted-block design with fixed block size of six; separate schedules were generated for each country. [REDACTED] Whilst block randomisation can be subject to bias, by having a separate schedule for each country, the chance of bias was reduced. As such, the EAG is satisfied that randomisation was carried out appropriately.
Allocation Concealment	METREO CSR, Section 4.5.3, p. 36 ⁷⁵	Appropriate The EAG is satisfied that the allocation of treatment was appropriately concealed and that participants and investigators remained blinded throughout the study, unless in the case of an emergency or serious medical condition. Study treatments were identical in appearance and were both administered as

Trial design or conduct concept	Section in the CS where methods are reported	EAG's assessment
		SC injection to ensure investigators and subjects remained blind.
Blinding	METREO CSR, Section 4.5.3, p.36 ⁷⁵	Appropriate The EAG is satisfied that appropriate measures were taken to ensure that the study remained blinded throughout. To ensure blinding of treatment allocations, mepolizumab was prepared at each site by a designated unblinded staff member who remained independent of study assessments. Unblinding was only permitted in the case of an emergency or in the event of a serious medical condition. Participants received either mepolizumab or placebo every 4 weeks through SC injection.
Statistical analyses	Appendix J, Section J.2.5, p. 23 ⁶⁴	Appropriate Multiplicity arising from the two treatment comparisons was controlled using the Hochberg testing procedure to control family-wise Type 1 error rate within an endpoint. A hierarchical approach to testing endpoints was used, whereby each endpoint was only tested if the previous endpoint was statistically significant. The EAG notes that METREO was only powered sufficiently to identify significant differences in the primary outcome (annualised rate of moderate to severe exacerbations), however, the EAG is satisfied that the Company's statistical analysis is appropriate.
Outcomes	Appendix J, Section J.2.1, Table, 8, p. 15 ⁶⁴	Appropriate METREO's primary outcome assessed the annualised rate of moderate/severe exacerbations from baseline to week 52. Other pre-specified outcomes included lung function and frequency of exacerbations resulting in hospital admission or ED visit. Additionally, validated tools were used to measure disease specific HRQOL and symptom control (COPD assessment test and SGRQ). Adverse effects of treatment were recorded which included all-cause mortality. Although the trial duration was insufficient to capture long-term outcomes, particularly mortality, the EAG is satisfied that all

Trial design or conduct concept	Section in the CS where methods are reported	EAG's assessment
		(except that the data were not analysed by CB status). The analyses were consistent with those pre-specified in the protocol. Sub-group analyses for the mITT-300 population, which represents the target group in the Company's submission, were undertaken in the MATINEE and pooled analyses.
Intervention	Appendix B, Section B.1.7 ⁵⁴ METREX CSR Section 4.2, p. 35 ^{15,76}	Appropriate Participants in the experimental arm received 100mg mepolizumab (SC injection) every 4 weeks in addition to standard of care (triple therapy, consisting of an inhaled corticosteroid [≥ 500 mcg/day fluticasone propionate or Equivalent] plus an inhaled LABA and an inhaled LAMA in the 3 months prior to visit 1) for 52 weeks. ^{68 69} Also, results from the METREO trial showed no evidence of greater effects of mepolizumab at higher doses. The EAG are satisfied that the intervention is consistent with the NICE scope and Marketing Authorisation.^{6,70}
Comparator	CS, Section 2.2, Table 5 ⁶	Appropriate Participants in the comparator arm received 100mg placebo (0.9% sodium chloride) (SC injection) every 4 weeks in addition to optimised standard of care (triple therapy, consisting of an inhaled corticosteroid [≥ 500 mcg/day fluticasone propionate or Equivalent] plus an inhaled LABA and an inhaled LAMA in the 3 months prior to visit 1) for 52 weeks. The EAG is satisfied that the comparator was appropriate and aligns with the NICE scope.⁶ The NICE scope also included dupilumab with double or triple therapy (subject to NICE evaluation),⁶ which was addressed by the Company in the ITCs (see Section 3.5).
Randomisation	Pavord et al. 2017	Appropriate

Trial design or conduct concept	Section in the CS where methods are reported	EAG's assessment
	Supplemental file, Section 5 – p. 14 ¹⁵	Randomisation was performed using a centralised, computer-generated, permuted-block schedule with a fixed block size of 6. Separate schedules were generated for each country, and each was stratified by blood eosinophil count (patients with ≥ 150 cells/μL at screening or ≥ 300 cells/μL in the previous year] or without [< 150 cells/μL at screening and no evidence of ≥ 300 cells/μL in the previous year] an eosinophilic phenotype). The EAG considers the randomisation approach used by the Company to be appropriate. Baseline characteristics were reasonably well-balanced between groups, which supports the effectiveness of the randomisation process.
Allocation concealment	METREX CSR Section 4.5.2, p. 40 ⁷⁶	Appropriate The EAG considers the allocation process appropriate, as it appears to have been fully automated, reducing the risk of interference or prediction by trial staff.
Blinding	METREX CSR, Section 4.5.3, p. 40 ⁷⁶	Appropriate The Company provided details of their blinding procedure, including details of which parties were blinded (investigators, subjects, and those involved in the administration of treatment and study assessments), how blinding was implemented and details of the emergency unblinding procedure, which adhered to the CONSORT reporting requirements.⁷⁷ The EAG is satisfied that this is appropriate.
Statistical analyses	Appendix J, Section J.2.5, pp. 21-23⁶⁴ CS, Section 2.6.3, Table 23⁶	Appropriate The primary endpoint—the annualised rate of moderate and severe exacerbations—was compared between the treatment and placebo groups using an ITT analysis. The α-level was split to account for two primary comparisons: $\alpha=0.04$ for the high-eosinophil group and $\alpha=0.01$ for the overall population, reducing the risk of false-positive results. If the overall population showed statistical significance at $\alpha=0.01$, the high-eosinophil group was then tested; otherwise, $\alpha=0.04$ applied. Secondary endpoints were assessed using a hierarchical testing procedure, with each analysed only if the preceding endpoint was significant.

Trial design or conduct concept	Section in the CS where methods are reported	EAG's assessment
		The EAG notes that METREX was only adequately powered to detect meaningful differences in the primary outcome—annualised moderate to severe exacerbation rates—within the originally planned study population (and not necessarily within the mITT-300 subgroup, although this was addressed through the pooled analysis). Nonetheless, the EAG considers the Company's statistical approach to be appropriate.
Outcomes	CS, Section 2.2, Table 5 ⁶	Appropriate The primary outcome for METREX was annualised rate of moderate/severe exacerbations at baseline to week 52. Other prespecified outcomes included time to first moderate/severe exacerbation, annual rate of COPD exacerbations requiring ED visit and/or hospitalisations and HRQoL (assessed using the SGRQ-C and CAT tools) and lung function. Adverse effects of treatment were recorded, which included all-cause mortality. Due to the relatively short length of the METREX trial for this chronic disease, the long-term impact on mortality is unknown. The EAG considers the outcomes assessed to be appropriate and in-line with the NICE scope.
Abbreviations: EAG = External Assessment Group; BCC = Best Care COPD program; CAT = COPD Assessment Test; CB = Chronic bronchitis; CFB = Change From Baseline; CONSORT = Consolidated Standards of Reporting Trials; COPD = Chronic Obstructive Pulmonary Disease; FEV = Forced Expiratory Volume; GOLD = Global Initiative for Chronic Obstructive Lung Disease; GSK = GlaxoSmithKline; HCRU = Health Care Resource Utilization; HRQOL = Health-Related Quality of Life; ICS = Inhaled corticosteroid; mITT-300 = modified intention-to-treat 300 (participants with BEC ≥300 cells/μL at screening who received ≥1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline); SC = subcutaneous; SGRQ = St. George's Respiratory Questionnaire – COPD specific		

Table 3:6: Summary of mITT-300 pooled analysis critique

Trial design or conduct concept	Section in the CS where methods are reported	EAG's assessment
Eligibility criteria	CS Section 2.2, Table 5 ⁶	Secondary Issue 7

Trial design or conduct concept	Section in the CS where methods are reported	EAG's assessment
		The trial eligibility of each trial was narrower than the NICE scope. Moreover, eligibility criteria varied across the trials in relation to patient eosinophil levels, asthma diagnosis and history, and smoking status. In MATINEE, moderate exacerbations required corticosteroids; antibiotics alone did not qualify unlike in METREX and METREO. Overall, these sources of heterogeneity could affect the precision of the pooled results. The EAG also notes that people with certain comorbidities were excluded from the clinical trials, which affects the representativeness of participants to UK clinical practice. See Section 3.2.1 and Section 1.4 for further details.
Subgroups	CS, Tables 1 and 31 ⁶ Pooled analysis CSR Section 1.4.3.4 ⁷⁸	Appropriate Sub-group analyses were undertaken for the primary outcome (annualised rate of moderate/ severe exacerbations) by baseline characteristics across trials for the mITT-300 population. All subgroup variables in the NICE scope (BEC ≥ 300 cells/μL, COPD severity, frequency of exacerbations within the previous 12 months, CB or not, and smoking status) were analysed. The EAG considers this appropriate.
Intervention	CS, Table 5 ⁶	Appropriate All three trials (METREX, METREO and MATINEE) had the same intervention (please see Tables 3.3-5, Intervention domain). The EAG are satisfied that the intervention is consistent with the NICE scope and Marketing Authorisation.^{6,70}
Comparator	CS, Table 5 ⁶	Appropriate All three trials overall had the same comparator arm (please see Tables 3.3-5, comparator domain). The EAG is satisfied that the comparator used in each trial was appropriate as clinical advice to the EAG confirmed that this was considered standard of care in UK practice.
Randomisation	CS, Table 9 ⁶	Secondary Issue 6

Trial design or conduct concept	Section in the CS where methods are reported	EAG's assessment
		The randomisation methods used in the individual trials were considered appropriate by the EAG. Furthermore, baseline characteristics were reasonably well balanced between the intervention and placebo groups in the pooled analysis. However, the pooled analyses only included a subset of participants from the METREX and METREO primary trials. This is problematic as it undermines the randomisation process. See Section 3.2.2 and Section 1.4 for further comment
Allocation concealment	NA	Please see comments for the individual (MATINEE, METREX and METREO) trials
Blinding	NA	Please see comments for the individual (MATINEE, METREX and METREO) trials
Statistical analyses	Sections 1.4 and 2.2.3, mITT-300 pooled analysis CSR ⁷⁸ CS, Table 13 ⁶	Secondary Issue 6 A pooled analysis was undertaken of efficacy data from the three trials including all randomised participants who received ≥ 1 dose of study treatment and with a screening BEC ≥ 300 cells/μL. Smoking status, disease severity, exacerbation history, geographic region and study were controlled for in the analyses as covariates. A pre-specified hierarchy was employed to account for multiplicity across the primary and secondary endpoints. The pooled analyses included only a subset of participants from the METREX and METREO trials, who matched the characteristics of patients in the MATINEE trial. The selective inclusion of participants in the pooled analysis could introduce selection bias. See Section 3.2.2 and Section 1.4 for further comment.
Outcomes	CS, Table 5 ⁶	Appropriate All efficacy outcomes from the NICE scope were included in the pooled analysis. The EAG note moderate exacerbations were defined as those leading to treatment with systemic glucocorticoid, antibiotic, or both, in METREX and METREO trials, while MATINEE, required systemic glucocorticoids. Following consultation with

Trial design or conduct concept	Section in the CS where methods are reported	EAG's assessment
		a clinical advisor the less stringent definition was confirmed to align with UK clinical practice and is therefore acceptable. AEs and deaths were not included for the pooled analysis, albeit they were captured in the reasons for study withdrawal. The analysis of AEs in the pooled analysis would have provided supportive information. However, as these data were reported for the individual trials, the EAG does not consider this to be of concern.
Abbreviations: BEC = blood eosinophil count; CS = company submission; EAG = External Assessment Group; NA = Not applicable.		

3.2.1 Eligibility criteria

The eligibility criteria across all pivotal trials (MATINEE, METREO and METREX) are consistent in age (adults ≥ 40 years), background therapy (using an ICS at a dose ≥ 500 mcg/day fluticasone propionate (FP) dose equivalent plus LABA plus LAMA for a minimum of 3 months prior to screening), severity (GOLD 2-4), and number and severity of exacerbations (≥ 2 moderate or ≥ 1 severe). Clinical advice to the EAG confirmed that these eligibility criteria are likely to be representative of the UK COPD population.

In Sections 2.1.1 and 2.2.3 the EAG noted that patients with certain comorbidities were excluded from the mepolizumab trials, which, although clinically justified, limits generalisability given the high prevalence of comorbidities in patients likely to receive add-on mepolizumab.¹³ Clinical advice to the EAG confirmed (if mepolizumab were recommended) that these patients would still be eligible for treatment in clinical practice and that there is a possibility that people with uncontrolled diabetes/cardiac disease may have worse outcomes. However, this would more likely be due to their co-morbidities and not due to their response to mepolizumab (see Secondary Issue 7; Section 1.4).

Differences between trials include study locations, as MATINEE recruited 23 participants (3%) in UK sites and METREO recruited 22 participants (3%)

while METREX did not include UK sites. However, clinical advice to the EAG confirmed that the baseline characteristics of participants in all three trials were representative of COPD patients who are seen in UK clinical practice on all variables apart from race, which is unlikely to affect the results. The BEC thresholds also varied between trials, with MATINEE using the most stringent criteria ($\geq 300/\mu\text{L}$ at screening and ≥ 150 cells/ μL in the prior 12 months), aligning with GOLD recommendations and therefore this was adopted by the Company for the mITT-300 pooled analysis. The EAG discusses the issue with inclusion of a restricted population in Section 3.2.2, below.

Asthma eligibility also varied between the trials. In all three trials patients with current asthma were excluded. In MATINEE, patients with former asthma were also excluded (some patients with former asthma were included in METREX and METREO). However, [REDACTED]

[REDACTED].⁷¹ Additionally, only MATINEE required participants to be current or former smokers (with ≥ 10 pack-years at screening).⁶⁴ Finally, in MATINEE moderate exacerbations were required to have been treated with corticosteroids; those treated with antibiotics alone did not qualify unlike in METREX and METREO. Clinical advice to the EAG confirmed exacerbations in practice were identified by reviewing General Practitioner (GP) records for antibiotic or corticosteroid treatment and that this approach was not very well standardised in clinic. Overall, although these sources of heterogeneity between the trials are not a major concern, they could still collectively affect the precision of the pooled analysis.

Finally, the EAG notes that the population specified in the Company decision problem is narrower than that in the NICE scope.³¹ This is addressed in Section 2.3.1.

3.2.2 Randomisation and statistical analyses

The analysis in MATINEE appears to have only been powered for the primary outcome, which was the annualised rate of moderate/severe COPD

exacerbations.⁶ Whilst powering a study for the primary outcome only is a common feature of clinical trials,⁷⁹ it means that the results in relation to other outcomes should be treated as exploratory. In METREO and METREX, the information provided by the Company (Table 12, Appendix J⁶⁴) suggests that the mITT-300 analysis for the primary endpoint was underpowered as an estimated 400 patients (200 patients per group) were required in METREX and 660 patients (220 patients in each group) in METREO to provide 90% power to detect a 35% decrease in the rate of moderate/severe exacerbations from 2.0 per year in the placebo group to 1.3 per year in the mepolizumab group.⁶⁴ The number of included participants was <100 in each group.⁶ The results can therefore only be treated as exploratory and should not be used as a basis for decision making. However, as stated by the Company in the CS “The core evidence supporting the clinical effectiveness of mepolizumab is drawn from a pooled analysis of the pooled mITT-300 population” (CS Section 2.5⁶). The sample sizes in the pooled analyses were significantly larger than for individual studies due to the pooling of data across the three primary clinical trials, which will have increased the sample size of the population of interest and increased the statistical power. However, the EAG notes that the pooled analyses only included a subset of participants from the METREX and METREO trials, who matched the characteristics of patients in the MATINEE trial. The selection of a patient subset undermines the randomisation process, meaning that the balance of prognostic factors may not be equally balanced between groups in the pooled analysis. The EAG did not identify notable differences in baseline characteristics between the primary studies and the pooled analysis, or between the intervention and placebo groups in the pooled analysis (CS Table 9⁶). However, this does not ensure comparability as unreported variables may have been imbalanced. Given the lack of randomisation of patients in the pooled analysis, and as the Company submitted the results from the pooled analysis as the core evidence supporting their submission, the EAG considers the inclusion of a patient subset in the pooled analysis to be a secondary issue (Secondary Issue 6; Section 1.4).

3.3 Critique of the results of the trials of the technology of interest

In CS Section 2.6 the Company outlines the primary and secondary endpoints for MATINEE (Section 2.6.1) and METREX and METREO (Section 2.6.2). Information on the mITT-300 pooled analysis for the primary endpoint is included in Section 2.6.3. Subgroup analyses for MATINEE are reported in Section 2.8.1 while subgroup analyses from METREX or METREO were not included in the CS as these were deemed not relevant for this appraisal, since the efficacy data representing the target population—patients with a screening BEC ≥ 300 cells/ μ L— constitute a subgroup within those trials.⁶

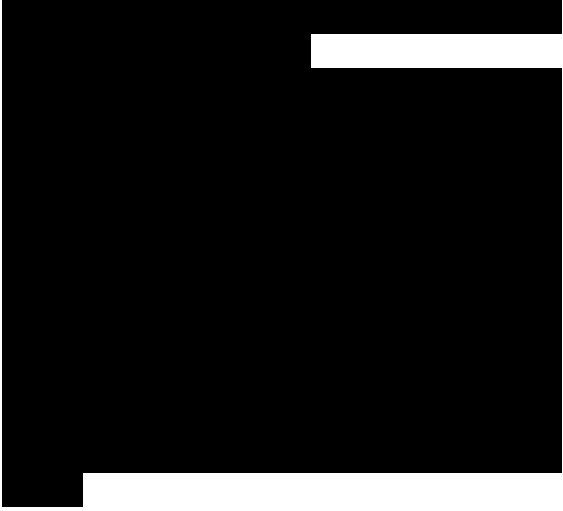
Table 3:6 below presents a summary overview of the EAG's assessment of trial results including the mITT-300 pooled analysis.

Table 3:6: Summary of EAG's assessment of trial results

Trial design or conduct concept	MATINEE	METREO	METREX	mITT-300 pooled analysis
Baseline characteristics	Appropriate	Some concerns	Some concerns	Appropriate
Drop-out rate	Appropriate	Some concerns	Some concerns	Some concerns
Lung function (FEV1, FV)	Appropriate	Outcome not assessed for the mITT-300 population	Outcome not assessed for the ITT-300 population	Appropriate
Frequency of moderate or severe exacerbations: Annualised rate of moderate or severe COPD exacerbations (Primary outcome)	Some concerns	Appropriate	Appropriate	Appropriate
Key secondary efficacy outcomes: Time to first moderate or severe exacerbation	Some concerns	Appropriate	Appropriate	Appropriate

Key secondary efficacy outcomes: Exacerbations requiring ED visit/hospitalisation	Appropriate	Appropriate	Appropriate	Appropriate
Symptom control: E-RS:COPD Score	Some concerns	Outcome not assessed	Outcome not assessed for the ITT-300 population	Outcome not assessed
Mortality	Appropriate	Outcome not assessed	Outcome not assessed	Outcome not assessed
Adverse events	Appropriate	Appropriate	Appropriate	Some concerns
Health-related quality of life (CAT and SGRQ)	Some concerns	Appropriate	Appropriate	Appropriate
Sub-group analyses	Some concerns	Outcome not assessed for the mITT-300 population	Outcome not assessed for the mITT-300 population	Some concerns
CAT = COPD Assessment Test; FEV1 = Forced Expiratory Volume in 1 Second; FVC = Forced Vital capacity; E-RS:COPD = Exacerbations of COPD Tool - Respiratory Symptoms; SGRQ = St. George's Respiratory Questionnaire; mITT-300 = modified intention-to-treat 300 (participants with BEC ≥ 300 cells/ μ L at screening who received ≥ 1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline)				

Table 3:7: Summary of Company interpretation of MATINEE trial results

Trial design or conduct concept	Section in the CS where methods are reported	MATINEE
Baseline characteristics	CS, Section 2.3.2.1, Table 8, pp. 65-67⁶ Sciurba et al, 2025, p. 1719 and Supplement Table S1¹⁴ CS, Section 2.5.1, p.79⁶	Appropriate Overall patient and disease baseline characteristics were generally balanced between groups. The study population was predominantly white (84%) and male (69%), with a mean age of 66.2 years; 61% were aged ≥65 years. Despite underrepresentation of minority ethnic groups, particularly Black patients, the EAG considers MATINEE broadly representative of UK COPD practice, though limited ethnic diversity remains a generalisability limitation.
Drop-out rate	MATINEE CSR, Section 4.1, pp.98-99⁷¹	Appropriate  The EAG identified no imbalance in dropout rates across treatment groups or study durations.
Lung function	CS, Section 2.6.1.3, Table 21⁶ MATINEE CSR Section 5.1.7., p. 178⁷¹	Appropriate Baseline lung function was well balanced between treatment groups. Changes from baseline in pre-bronchodilator FEV1 and FVC at Weeks 24 and 52 were small and broadly similar between mepolizumab and placebo indicating no meaningful treatment effect on lung function over this period. The EAG considers the lack of a statistically significant effect on lung function unsurprising and consistent with mepolizumab's mechanism of action to reduce eosinophils; however, the outcome appears underpowered, and any conclusions should therefore be interpreted

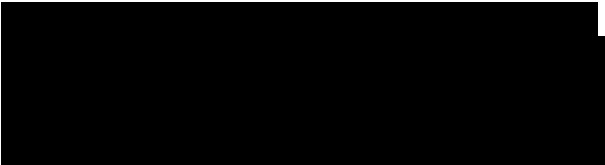
Trial design or conduct concept	Section in the CS where methods are reported	MATINEE
		as supportive rather than indicative of a meaningful treatment effect.
Frequency of moderate or severe exacerbations: Annualised rate of moderate or severe COPD exacerbations	MATINEE CSR, Section 5.1.1. Table 23 and Table 24 pp. 122-126 Section 5.1.2.2.5, Table 27, p. 131 ⁷¹ CS, Section 2.6.1.1, p. 80 Sciurba et al., 2025, Table 2 ¹⁴	Some concerns In MATINEE this is the primary outcome. At Week 104, mepolizumab demonstrated a statistically significant 21% reduction in the annualised rate of moderate/severe exacerbations compared with placebo in the mITT population (RR 0.79; 95% CI 0.66–0.94; p=0.011). Despite these findings, the EAG notes inclusion of a minority of patients in the mITT population with asthma and unequal trial participation lengths arising from COVID-19–related disruptions may have confounded the observed treatment effect, limiting confidence in the robustness and interpretability of the results. See Section 3.3.3 for further comment.
Frequency of exacerbations resulting in hospital admission or emergency department visit	CS, Section 2.6.1.2.5, p. 85 ⁶	Appropriate The annualised rate of exacerbations leading to an ED visit, hospitalisation, or both was 0.13 events per year with mepolizumab and 0.20 events per year with placebo (RR 0.65 [95% CI: 0.43, 0.96]). By week 104 the mITT MATINEE participants (n=403 mepolizumab; n=401 PBO) free of exacerbations requiring ED visit were ██████ in mepolizumab group and ██████ in the PBO group. The EAG has no concerns regarding the Company’s analytical approach for this endpoint.
Symptom control (E-RS:COPD Score)	CS, Section 2.6.1.2.4, Table 19, pp.83-84 ⁶ Sciurba et al., 2025 ¹⁴ MATINEE CSR, p. 1025 ⁷¹	Some Concerns E-RS:COPD outcomes showed no meaningful benefit of mepolizumab over placebo. Response rates were similar between groups (31% vs 34%; OR 0.82, (95% CI 0.60, 1.12), p=0.209), with minimal and non-significant differences in mean change from baseline ██████. A ██████ proportion of participants in the mepolizumab group experienced no improvement or worsening symptoms ██████. The EAG is concerned over the lack of Week 104 E-RS:COPD data in the mITT population which limits

Trial design or conduct concept	Section in the CS where methods are reported	MATINEE
		assessment of longer-term effects. See Section 3.3.6 for further discussion.
Mortality	MATINEE CSR, Section 5.2.3.1, p. 194 ⁶	Appropriate Mortality data was not included in the CS. In MATINEE, mortality was studied as part of the safety analysis. [REDACTED] The EAG is not concerned that mortality data were not included in the CS, as deaths were assessed within the safety analysis, were balanced between groups ([REDACTED]), and none were considered treatment-related; however, this limits interpretation to safety rather than efficacy.
Adverse effects of treatment	CS, Section 2.11.1.1, Table 36, Table 37 and Table 38 pp. 128-129 ⁶	Appropriate Safety data were assessed for all randomised patients who received at least one dose of study treatment. Overall, safety findings were consistent with the established safety profile of mepolizumab.¹⁴ The mean duration of exposure was 15 months in both treatment arms. The incidence and event rates of on-treatment AEs, serious adverse events (SAEs), and Adverse Event of Special Interest (AESI) were generally comparable between groups. [REDACTED] Given the small numbers involved, the EAG does not consider these imbalances to be clinically meaningful.
Health-related quality of life (CAT and SGRQ-C Scores)	CS, Section 2.6.1.2.2, Table 17, p. 83. Section 2.6.1.2.3, Table 18, p. 84. Section 5.1.3.1, Table 36, p. 157 ⁶	Some concerns The CS concluded a trend of improvement in HRQoL was observed in the mepolizumab group, based on a numerically higher mean decrease in SGRQ total score from baseline to Week 52. However, no significant difference was shown. Furthermore, no difference was

Trial design or conduct concept	Section in the CS where methods are reported	MATINEE
	MATINEE CSR, Section 5.1.4.1, Table 38, p. 162. MATINEE CSR, Section 5.1.4.2., Table 40, p. 167 ⁷¹	observed in CAT or EQ-5D-3L health state index scores between treatment groups. The EAG requested supplementary information in the PfC (question A5), and the Company subsequently submitted further data.¹² The EAG notes that patients with more severe disease (GOLD 4) showed a smaller improvement in HRQoL with mepolizumab, as placebo-treated patients in this group experienced more favourable outcomes. See Section 3.3.6 for further details.
Key secondary efficacy outcomes: Time to first moderate or severe exacerbation	CS, Section 2.6.1.2.1 Table 16, p.81 ⁶	Some concerns Mepolizumab significantly delayed time to first moderate or severe exacerbation versus placebo through Week 104 (median 419 vs. 321 days; HR 0.77, (95% CI 0.64, 0.93), p=0.009), with fewer patients experiencing an exacerbation over follow-up. At Week 52, 172 mepolizumab and 146 placebo patients remained exacerbation-free; by Week 104, [REDACTED], patients respectively, had experienced a first moderate/severe exacerbation. The EAG is concerned the dual-duration design may bias results, as COVID-19 likely reduced exacerbations in the 52-week group and fitter or early responders continuing to 104 weeks may have inflated mepolizumab's apparent benefit. Please see Section 3.3.4 for further details.
Key secondary efficacy outcomes: Mortality	MATINEE CSR, Section 5.2.3.1, p. 194 ⁷¹	Appropriate Mortality data was not included in the CS. In MATINEE, mortality was however studied as part of the safety analysis. [REDACTED] The EAG is not concerned because deaths were balanced between groups, few in number, and none were treatment-related, indicating no mortality safety signal despite their exclusion from the CS.

Trial design or conduct concept	Section in the CS where methods are reported	MATINEE
Subgroup analyses	Sciurba et al., 2025 ¹⁴	Some concerns Pre-specified subgroup analyses were performed for the primary efficacy outcome although Sciurba et al. recommend they should not be used for inference due to the lack of adjustment for multiplicity.¹⁴ Significant reductions were observed in 13 out of 40 predefined subgroups, these results may reflect limited power within subgroups and a potentially unstable pattern of significance. The EAG notes that these findings limit the confidence in the robustness and generalisability of the effects. See Section 3.3.7 for further discussion on this point.
Abbreviations: AE = adverse event; AESI = Adverse Event of Special Interest; CI = confidence interval; CS = company submission; ED = emergency department; EAG = External Assessment Group; GOLD= Global initiative for Chronic Obstructive Lung Disease; HRQoL = health-related quality of life; KM = Kaplan–Meier; LS = Least Square; mITT = modified intention-to-treat; mMRC = modified Medical Research Council dyspnoea scale; PBO = Placebo; RR = Rate Ratio; SAE = Serious Adverse Event.		

Table 3:8: Summary of Company interpretation of METREX trial results

Trial design or conduct concept	Section in the CS where methods are reported	METREX
Baseline characteristics	CS, Section 2.3.2.3, Table 9 ⁶	Some concerns Patient characteristics were generally well-balanced between the mepolizumab 100mg and placebo trial arms for the mITT-300 subgroup. However, imbalances were observed for the proportion of patients with mMRC <2, the proportion of patients with mMRC ≥2 and the proportion of never smokers. The company did not report the rates of different inhaler combinations or the proportion of participants in each trial arm who received the “five fundamentals of COPD care”. See Section 3.3.1 for further comment.
Dropout rate	Pooled analysis CSR Tables 16 and 17 ⁷⁸	Some concerns 

Trial design or conduct concept	Section in the CS where methods are reported	METREX
		Please see Section 3.3.2 for further comment
Lung function	Outcome not assessed	Lung function was not assessed as an outcome for the mITT-300 subgroup.
Frequency of moderate or severe exacerbations: Annualised rate of moderate or severe COPD exacerbations	CS Section 2.6.3.2, Table 22 ⁶	Appropriate In the mITT-300 subgroup, there was [REDACTED] in the annualised rate of moderate/severe exacerbations for mepolizumab compared with placebo [REDACTED]. The EAG is satisfied with the assessment of this outcome. As discussed in the methods Section (Section 3.3.2), this analysis was underpowered and therefore the results may be unreliable. The EAG is unable to comment on whether the result indicates a clinically minimum important difference (CMID) due to a lack of validated threshold for this outcome, as confirmed by clinical advice to the EAG. This was discussed in a single technology appraisal on a related topic²⁵ and will not be re-addressed here. This also applies to the secondary exacerbation outcomes in this table.
Time to first moderate or severe exacerbation	CS, Section 2.6.3.2, Table 23 ⁶	Appropriate In the mITT-300 subgroup, the probability of having a moderate/severe exacerbation was [REDACTED] in the mepolizumab group compared with the placebo group with a HR of [REDACTED] The EAG is satisfied with the assessment of this outcome. As discussed in the methods Section (Section 3.3.2), this analysis was underpowered and therefore the results may be unreliable.
Frequency of exacerbations resulting in hospital admission or	CS, Section 2.6.3.3, Table 24 ⁶	Appropriate The results show

Trial design or conduct concept	Section in the CS where methods are reported	METREX
emergency department visit		[REDACTED]. This may reflect that these analyses were underpowered due to the small numbers of participants who experienced this outcome. This issue has been discussed in the in the methods Section 3.2.2 and will not be re-addressed here.
Symptom control (E-RS:COPD Score)	Outcome not assessed	E-RS:COPD was not reported for the mITT-300 subgroup
Mortality	Outcome not assessed	Mortality was not reported as a secondary outcome for the mITT-300 subgroup, however, this outcome was captured in the AE data.
Adverse events of treatment	CS, Table 39, Section 2.1.1.2 ⁶	Appropriate AEs data were reported for the safety population as opposed to the mITT-300 subgroup. The Company stated that this was because safety does not vary by eosinophil levels. The incidence of any AEs was 80% in the mepolizumab arm and 82% in the placebo arm; the incidence of SAEs was 28% in the mepolizumab arm and 31% in the placebo arm; the incidence of death was 4% in both arms and the incidence of events leading to treatment discontinuation was 7% in the mepolizumab arm and 8% in the placebo arm. The EAG is satisfied that the AEs assessed were appropriate and that the rates of AEs were sufficiently well-balanced between trials arms.
Health-related quality of life (CAT and SGRQ-C Scores)	CS, Section 2.6.3.5, Tables 26 – 29 ⁶	Appropriate [REDACTED] The EAG is satisfied that the measures used to assess quality of life in the METREX trial and the CMID thresholds were appropriate, albeit that the results were non-significant, possibly reflecting the lack of statistical power in these analyses as discussed in the methods Section.

Trial design or conduct concept	Section in the CS where methods are reported	METREX
Sub-group analyses	Outcome not assessed	Sub-group analyses were not reported for the METREX ITT-300 subgroup.
Abbreviations: CAT = COPD assessment test; CI = confidence interval; CMID = clinically minimum important difference; CS = company submission; CSR = clinical study report; ED = emergency department; FEV = forced expiratory volume; FVC = forced vital capacity; OR = odds ratio; RR = relative risk; SGRQ = St. George's Respiratory Questionnaire.		

Table 3:9: Summary of Company interpretation of METREO trial results

Trial design or conduct concept	Section in the CS where methods are reported	METREO
Baseline characteristics	Appendix J, Section J.2.2.3, Table 9, p 76	Some concerns Baseline characteristics were generally balanced between the mepolizumab and placebo groups in METREO. However, the EAG noted some differences in proportion of males and females between the two groups. The clinical expert advised the EAG that sex is an effect modifier in COPD, and as such, the EAG has some concerns. Please see Section 3.3.1 for further details.
Dropout rate	METREO CSR. Section 5.1.2. Table 2. p. 62	Some concerns There was a [REDACTED] The primary reason for study withdrawal was [REDACTED] Differential drop-out rate can introduce bias to treatment effect estimation. Baseline characteristics were not reported, as such the EAG is unable to assess if the characteristics of the participants were well balanced following drop-out. Please see Section 3.2.5 for further comment

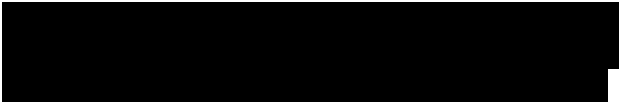
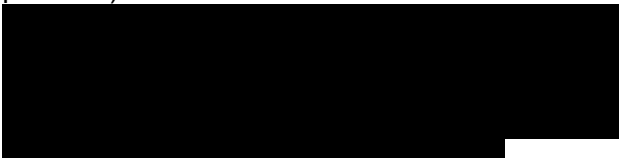
Trial design or conduct concept	Section in the CS where methods are reported	METREO
Primary efficacy outcome: Annualised rate of moderate or severe COPD exacerbations	CS Section 2.6.3.2, table 22, p. 87. Appendix J.2.6, table 13, p. 24	Appropriate In the METREO mITT-300 subgroup the annualised rate of moderate or severe exacerbations was [REDACTED]. The EAG is satisfied with the assessment of this outcome. As discussed in the methods section (Section 3.3.2), this analysis was underpowered and therefore the results may be unreliable.
Key secondary efficacy outcomes: Time to first moderate or severe exacerbation	CS Section 2.6.3.2, Table 23, p. 88	Appropriate In the METREO mITT-300 subgroup the Week 52 probability (%) of an exacerbation was [REDACTED] (95% CI [REDACTED]) in the mepolizumab group and [REDACTED] (CI [REDACTED]) in the placebo group.. The HR was [REDACTED] (95% CI [REDACTED], [REDACTED], [REDACTED]). The EAG is satisfied with the assessment of this outcome, however the analysis was underpowered (see Section 3.3.2).
Key secondary efficacy outcomes: Exacerbations requiring ED visit/hospitalisation	CS, Section 2.6.3.3, Table 24	Appropriate The annualised rate of exacerbations requiring hospitalisation or ED visit was [REDACTED] for the mITT-300 subgroup. However, confidence intervals were not reported for this outcome. The EAG is satisfied with the assessment of this outcome, however the analysis was underpowered (see Section 3.3.2).
HRQOL: St. George Respiratory Questionnaire (SGRQ) total responders	CS, Section 2.6.3.6.1, Table 28, p. 99	Appropriate In METREO (mITT-300 subgroup), [REDACTED]. Non-response was higher in the placebo group [REDACTED].

Trial design or conduct concept	Section in the CS where methods are reported	METREO
		[REDACTED] No RR was reported for this outcome. The EAG is satisfied that the measures used to assess quality of life in METREO were appropriate, albeit that the results were non-significant, possibly reflecting the lack of statistical power in these analyses as discussed in the methods Section.
HRQoL: St. George's Respiratory Questionnaire-COPD (SGRQ-C) change from baseline	CS, Section 2.6.3.6.2, Table 29, p.101	Appropriate In METREO (mITT-300 subgroup), both treatment arms showed improvements in SGRQ-C scores by Week 52. Mepolizumab produced a least-squares mean change of [REDACTED] units; however, the [REDACTED]. The EAG is satisfied that the measures used to assess quality of life in METREO were appropriate, albeit that the results were non-significant, possibly reflecting the lack of statistical power in these analyses as discussed in the methods section.
Adverse events	CS, Section 2.11.2.1, Table 39, p. 130	Appropriate AEs in the safety population (not restricted by BEC threshold because safety was not considered by the company to vary by eosinophil level) were broadly similar between the mepolizumab and placebo group. AEs were experienced in 86% of the mepolizumab group and 82% of placebo group leading to 4% and 12% respectively, discontinuing treatment. Any SAEs were 26% in mepolizumab group and 30% in the placebo group. The EAG are satisfied that the AEs assessed in METREO were appropriate and that AEs were balanced between the mepolizumab and placebo group.
HRQoL: CAT total score responders	CS, Section 2.6.3.5.1, Table 26, p. 95	Appropriate [REDACTED]

Trial design or conduct concept	Section in the CS where methods are reported	METREO
		The EAG considers the quality-of-life measures in METREO appropriate, though the non-significant results may reflect limited statistical power, as noted in the methods.
HRQoL: Change from baseline in CAT score	CS, Section 2.6.3.5.2, Table 27, p. 97	Appropriate There was [REDACTED] The EAG considers the quality-of-life measures in METREO appropriate, though the non-significant results may reflect limited statistical power, as noted in the methods.
Results – Subgroup analysis	Outcome not assessed	Outcome not assessed No subgroup analysis was undertaken in the mITT-300 population within METREO.
Abbreviations: AE = adverse event; CAT = COPD assessment test; CI = confidence interval; CMID = clinically meaningful important difference; CS = company submission; EAG = External Assessment Group; HRQoL = health-related quality of life; mITT = modified intention to treat; PBO = Placebo; RR = risk ratio SQRQ = St George respiratory questionnaire.		

Table 3:10: Summary of Company interpretation of mITT - 300 pooled analyses trial results

Trial design or conduct concept	Section in the CS where methods are reported	mITT- 300 pooled analysis
Baseline characteristics	CS, Section 2.3.2.3, Table 9 ⁶	Appropriate Baseline characteristics were well-balanced between the mepolizumab and placebo groups. The greatest difference was a 6% higher rate of patients aged ≥65 years in the mepolizumab group and a 6% lower rate of patients aged 40 to <65 years in the mepolizumab group compared to the placebo group. However, the average age was well-balanced between groups (65.7 years for mepolizumab; 66.1 years for placebo).
Drop-out rate	CSR Tables 16 and 17 ⁷⁸	Some concerns [REDACTED] These study completion rates were acceptably high⁸⁰ and well-balanced between the groups. [REDACTED]. The proportions of patients discontinuing treatment were however well balanced between the groups. It is unclear how well-balanced patient characteristics were between the mepolizumab and placebo arms post-treatment discontinuation. Please see Section 3.3.2 for further comment.
Lung function	CSR, Table 41 ⁷⁸	Appropriate [REDACTED] The Company noted that the results are indicative of poor lung function across the trial cohort. The EAG are satisfied with the methods used to assess lung function. However, the wide confidence intervals indicate a lack of precision in this outcome.
Frequency of moderate or severe	CS Section 2.6.3.1, Table 22 ⁶	Appropriate

Trial design or conduct concept	Section in the CS where methods are reported	mITT- 300 pooled analysis
exacerbations: Annualised rate of moderate or severe COPD exacerbations		For the pooled mITT-300 population, the results showed a statistically significant reduction in this outcome RR 0.79 (0.68, 0.91); p=0.002. As previously noted, the EAG is unable to comment on whether the result indicates a CMID due to a lack of validated threshold for this outcome, as confirmed by clinical advice to the EAG. This was discussed in a single technology appraisal on a related topic ²⁵ and will not be re-addressed here. This also applies to the secondary exacerbation outcomes in this table.
Time to first moderate or severe exacerbation	CS, Section 2.6.3.2, Table 23 ⁶	Appropriate For the pooled mITT-300 population, the results showed 
Frequency of exacerbations resulting in hospital admission or emergency department visit	CS, Section 2.6.3.3, Table 24 ⁶	Appropriate The results from the pooled mITT-300 population across studies  in the rate of exacerbations requiring ED visit and/or hospitalisation (RR 0.71; 95% CI 0.51, 0.98; p=0.038) 
Symptom control (E-RS:COPD Score)	Outcome not assessed	E-RS:COPD was not assessed for the pooled mITT-300 population
Mortality	Outcome not assessed	Mortality was not assessed for the pooled ITT-300 population.
Adverse effects of treatment	CSR, Tables 16-17 ⁷⁸	Some concerns Safety data were not reported for the pooled mITT-300 population except for the proportions of patients who withdrew from studies or who discontinued treatment due to AEs or deaths. See Section Error! Reference source not found. for further comment
Health-related quality of life (CAT and	CS, Section 2.6.3.5.2, Table 26-29 ⁶	Appropriate A trend of improved HRQoL was observed in the mepolizumab group compared to the placebo group based on a greater mean

Trial design or conduct concept	Section in the CS where methods are reported	mITT- 300 pooled analysis
SGRQ-C Scores)		reduction in CAT score and a higher rate of SGRQ total responders from baseline to Week 52. A significantly greater reduction in SGRQ total score was found, favouring mepolizumab. However, there was a non-significantly lower proportion of CAT total responders in the mepolizumab vs the placebo group. The EAG are satisfied with the methods used to assess quality of life outcomes.
Sub-group analyses	Pooled ITT-300 CSR, Table 44 CS, Table 31, pg. 109 ⁶	Some concerns severity of airflow limitation (Severe: $\geq 30\%$-$<50\%$ predicted) The EAG is satisfied that the factors included in the sub-group analyses were appropriate, reflecting prognostic factors recognised in COPD. However, it is plausible that some findings reached statistical significance by chance alone, given the large number of analyses performed. See Section 3.3.7 for further comment.
Abbreviations: CAT = COPD assessment test; CI = confidence interval; CMID = clinically meaningful important difference; CSR = company study report; ED = emergency department; FEV = forced expiratory volume; FVC = forced vital capacity; HR = hazard ratio; NA = not applicable; OR = odds ratio; RR = relative risk; SGRQ = St. George's Respiratory Questionnaire.		

3.3.1 Baseline characteristics

Clinical advice to the EAG indicated that the baseline characteristics of MATINEE, METREX and METREO were broadly reflective of the population seen in UK clinical practice. However, the EAG note some minor imbalances between treatment arms in each of the trials as follows. In the mITT-300 subgroup of the METREO trial, the proportion of females was higher in the 100 mg mepolizumab arm compared to the placebo arm (40% vs 32%), while the proportion of males was lower (60% vs 68%). Males with COPD generally

have a worse prognosis than females, therefore this imbalance is likely to favour mepolizumab.

In the mITT-300 subgroup of the METREX trial, there was a higher proportion of patients with mMRC ≥ 2 , indicating more severe dyspnoea (breathlessness), in the 100mg mepolizumab arm compared to the placebo arm. Also, the proportion of never smokers – which is prognostic for better COPD-related health outcomes compared to current smokers,⁸¹ was lower in the 100mg mepolizumab arm compared to the placebo arm (1% versus 8%, respectively). Both imbalances favour the placebo group as opposed to the mepolizumab group.

The trial eligibility criteria did not require that participants use a specific ICS/LABA and LAMA SoC regimen. Clinical advice to the EAG suggests that a closed triple regimen (three drugs in one inhaler device) may be more effective than an open triple regimen (combination of ICS/LABA and LAMA in two separate devices). Hence, if the proportions of patients in the mepolizumab and placebo arms who were using closed versus open triple regimens varied (which the EAG are unable to verify as baseline data on variable were not provided by the Company), this could have impacted the results. It is also unknown if specific types of SoC medication and dosages were equally distributed between the mepolizumab and placebo groups in each trial and if these were representative of UK practice. The EAG notes that a lack of standardisation and reporting of SoC and additional treatments is a wider issue with clinical trial design and reporting and is not specific to this appraisal.

MATINEE was undertaken during COVID, prompting the Company to extend follow-up to up to 104 weeks, with baseline characteristics of fixed- and variable-duration participants provided in response to the EAG's request (PfC response, question A.7). Table 3:11 presents participant characteristics in the fixed and variable length groups.¹² The EAG did not identify any meaningful imbalances in baseline characteristics, with the exception of ethnicity by

treatment duration. Specifically, the proportion of Hispanic/Latino participants was higher in the variable-duration groups than in the fixed-duration groups (██████████). Conversely, White participants were less represented in the variable-duration groups compared with the fixed-duration groups (██████████).

Table 3:11: MATINEE participant baseline characteristics up to 52 weeks fixed duration and 104 weeks variable duration (mITT population)

Characteristic	Enrolled up to 52 weeks fixed duration		Enrolled up to 104 weeks variable duration	
	Placebo (N=175)	Mepo (N=170)	Placebo (N=226)	Mepo (N=233)
Age				
Mean (SD)	██████	██████	██████	██████
Median (min, max)	██████	██████	██████	██████
Age group years, n (%)				
<40	█	█	█	██
40 to <65	██	██	██	██
≥65 years	██	██	██	██
Sex, n (%)				
Female	██	██	██	██
Male	██	██	██	██
Ethnicity, n (%)				
Hispanic or Latino	██	██	██	██
Not Hispanic or Latino	██	██	██	██
Race, n (%)				
American Indian/Alaskan Native	██	██	██	██
Asian	██	██	██	██
Black or African American	██	██	██	██
Native Hawaiian or Other Pacific Islander	█	█	█	█
White	██	██	██	██
Mixed Race	██	██	██	█
Height (cm) mean (SD)	██████	██████	██████	██████
Weight (kg) mean (SD)	██████	██████	██████	██████

Characteristic	Enrolled up to 52 weeks fixed duration		Enrolled up to 104 weeks variable duration	
BMI kg/m ² mean (SD)				
Duration of COPD ≥10 years n (%)				
Mean duration of COPD (years [SD])				
Severity of airflow limitation [†] , n (%)				
Mild ≥80% predicted				
Moderate: ≥50% <80% predicted				
Severe: ≥30% <50% predicted				
Very severe: <30%				
CV comorbidity [‡] , n (%)				
Other comorbidity [¶] , n (%)				
mMRC score at screening, n (%)				
mMRC <2				
mMRC ≥2				
Missing				
Ever diagnosed with GERD, n (%)				
Number of moderate/severe exacerbations, mean (SD)				
Abbreviations: BMI = Body Mass Index; CV = Cardio Vascular; GERD = Gastroesophageal Reflux Disease; mMRC = modified Medical Research Council dyspnoea score; SD = Standard Deviation. Source: GlaxoSmithKline. Mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237] Company response to clarification questions. ¹²				

Finally, the distribution of different SoC regimens and the receipt of the five COPD fundamentals recommended by NICE⁸² (which may act as effect modifiers) was not reported for each group. However, the randomisation process may have equally distributed these interventions between the trial arms in each study. The EAG is unable to assess the impact of these issues on the results.

3.3.2 Drop-out rate

The overall study withdrawal rate was

[REDACTED]

However, in the METREO trial, for the mITT-300 subgroup, there was variation in withdrawal rates between those receiving 100mg mepolizumab (■% withdrawal) versus placebo (■% withdrawal). Similarly, treatment discontinuation was lower in patients who received mepolizumab 100mg, with ■% of patients in this group prematurely discontinuing treatment (■% withdrawing from the study at the same time) compared to ■% in the placebo group prematurely discontinuing treatment (■% withdrawing from the study at the same time).

[REDACTED]

[REDACTED]

■ It is unclear how well-balanced patient characteristics were between the mepolizumab and placebo arms post-study withdrawal (METREO) and treatment discontinuation (METREX and METREO). This can lead to attrition bias, whereby differences in patient characteristics post-study withdrawal / discontinuation can distort the perceived effectiveness of the intervention.

Additionally, higher effectiveness at 104 weeks may reflect differences in the patients who remained in the trial compared with those whose follow-up ended at 52 weeks. Participants continuing to 104 weeks are likely to be healthier, more adherent, and more engaged with COPD fundamentals of care. In contrast, patients who discontinued earlier may have had poorer health, lower adherence, or less benefit. This attrition or survivor bias can enrich the later cohort with patients more likely to respond, leading to higher observed effectiveness at 104 weeks.

3.3.3 Primary efficacy outcome

The EAG considered that the post-study withdrawals (METREO), treatment discontinuation (METREX) and differences in follow up (MATINEE) explained

above may have increased the uncertainty in the effectiveness of mepolizumab versus placebo and sought further clarification from the Company. Furthermore, the primary endpoint was underpowered for the mITT-300 populations in the METREO and METREX trials, meaning that results are exploratory – as are the secondary endpoints.

3.3.4 Secondary exacerbation outcomes

The EAG notes that the analysis of the primary endpoint in MATINEE and the results from the pooled analyses were the only analyses of exacerbation outcomes that were sufficiently powered for the mITT-300 population of interest in the CS.

The EAG has concerns about potential bias in the analysis of MATINEE's time to first moderate or severe exacerbation given the trial's dual-duration design. As discussed in Sections 3.3.1 and 3.3.3, both reduced exacerbation rates during the pandemic and selection/ attrition bias linked with the variable duration may have distorted the observed treatment effect across duration groups.

3.3.5 AEs

Safety analyses were not undertaken for the pooled analysis, albeit they were available for the MATINEE, METREX and METREO clinical trials. Rates of different types of adverse event were variable across the trials for certain outcomes (e.g., “*any [adverse] event*” occurred in 74%, 80% and 86% of patients who received mepolizumab in the MATINEE, METREX and METREX trials, respectively). This variability may reflect the small number of participants who experienced each outcome in the individual trials, and a pooled analysis of safety outcomes may have increased the precision of the data.

3.3.6 HRQoL outcomes

In line with the NICE scope, the trials assessed HRQoL. This was assessed as secondary outcomes in MATINEE (CAT, SGRQ-c and E-RS:COPD),

METREO (CAT and SGRQ-C) and METREX (CAT and SGRQ-C). Pooled results for E-RS:COPD were not available as this score was only evaluated in MATINEE. In MATINEE health-related outcomes were assessed from baseline up to Week 52 and Week 104, while in METREO and METREX outcomes were only assessed up to Week 52. The pooled mITT-300 analysis was performed on data up to Week 52.

A response was defined as a decrease of at least 2 points in the CAT score from baseline to Week 52. For the SGRQ-C a response was defined as a difference of at least 4 points from previous scores.^{72,73}

Across all three pivotal trials, the Week 52 OR for response was not statistically significant for the mepolizumab groups. Similarly, the pooled mITT-300 analysis of CAT scores showed no statistically significant improvement with mepolizumab compared with placebo

[REDACTED] (CS, Table 26, pg. 96).⁶

Similar lack of statistically significant results was observed in change from baseline in the CAT score across all individual trials and in the pooled mITT-300 analysis [REDACTED] (CS, Table 27, p. 98).⁶ Across the trials, Week-52 SGRQ-C outcomes consistently favoured mepolizumab. In the pooled mITT-300 population, results aligned with MATINEE: SGRQ scores improved more with mepolizumab (−7.1) than placebo (−4.9), yielding a treatment difference of −2.2 (95% CI −4.14 to −0.24; p=0.028) (CS, Table 29, pg. 102).⁶

The EAG understands that the lack of precision might be triggered by lack of power of the trials and the mITT-300 pooled population, however, the EAG is concerned that HRQoL scores were averaged across heterogeneous populations; which might not be representative of the HRQoL in participants with extreme scores at baseline. The proportion of CAT responders in MATINEE was numerically lower in the mepolizumab group. The non-significant OR (0.81; 95% CI includes 1) indicates no evidence of benefit in health status at Week 52. This suggests the treatment may not meaningfully

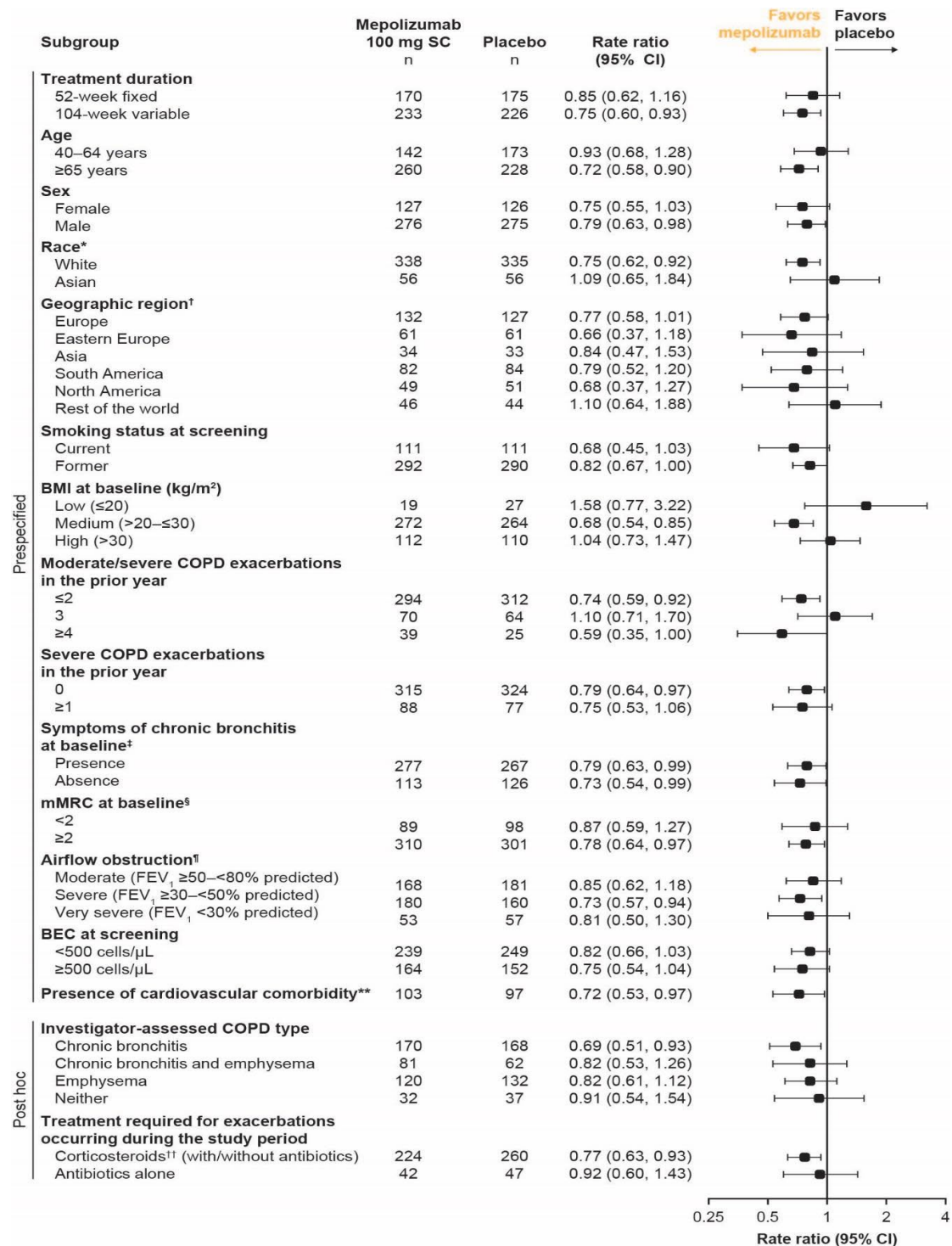
improve symptoms as experienced by patients. According to the professional organisation submission to this STA, the ARNS) suggests a clinically significant treatment response should include a demonstrable improvement in patient-reported quality of life and daily functioning.¹⁹

3.3.7 Subgroups

MATINEE studied the key outcome of annualised rate of moderate/severe exacerbation by subgroups (including treatment duration, age, sex, race, geographic region, smoking status at screening, BMI at baseline, moderate/severe COPD exacerbations in the prior year, severe COPD exacerbations in the prior year, symptoms of CB, mMRC at baseline, airflow obstruction, BEC at screening and presence of CV comorbidity) and presented the results in Supplemental material in Sciurba et al., 2025.¹⁴ Overall, the subgroup evidence across MATINEE, and the pooled mITT-300 population raises consistent concerns about reliability and interpretability. Many subgroup analyses were underpowered, and confidence intervals were often wide due to low participant numbers. Several analyses were post hoc (investigator-assessed COPD type and treatment required for exacerbations occurring during the study period) or done within already-restricted subgroups, increasing the risk of bias and undermining the protections of randomisation. The lack of multiplicity adjustment further limits the strength of any positive findings.⁸³ Furthermore, according to CONSORT guidelines for reporting of RCTs any secondary analyses should be pre-specified in the protocol, and if post-hoc analyses are being conducted this should be stated as strictly “hypothesis-generating” however, the Company has not provided that explanation on the subgroup analyses undertaken.⁷⁷ Together, these issues mean that the true pattern of treatment effects across subgroups remains uncertain, and the available analyses cannot confidently establish whether mepolizumab is consistently effective across different patient groups. The EAG recommends the interpretation of this information with caution and for these analyses to be taken as explorative.

The prespecified and post-hoc analyses shown below in Figure 3.1, presents results of showing that 14 of the 40 subgroup analyses achieved statistical significance in favour of mepolizumab (namely 104 weeks treatment duration, people aged ≥ 65 years, males, White, medium BMI, ≤ 2 moderate/ severe COPD exacerbations in previous year, no severe COPD exacerbations in previous year, presence and absence of CB at baseline, ≥ 2 mMRC scores, severe airflow obstruction and in people with CV comorbidity, investigator assessed CB, and people who received corticosteroids). The Company declares that CIs were not adjusted for multiplicity and also states that they should not be used to infer definitive treatment effects; the EAG agrees with this statement.¹⁴ It remains uncertain whether mepolizumab would have demonstrated effectiveness in additional subgroups had the sample size been larger. Clinical advice to the EAG confirmed that age, CB type of COPD, patients that received corticosteroids for exacerbation treatment and smoking cessation interventions are the most clinically meaningful subgroups from these analyses. The EAG recommends caution when interpreting these findings due to their exploratory nature.

Figure 3.1: Annualised rate of moderate/severe exacerbations by subgroup (MATINEE)



Abbreviations: BMI = Body Mass Index; CI = Confidence Interval; FEV₁ = Forced Expiratory Volume per 1 minute; Kg/m² = kilogram per square meter; SoC = Standard of Care.
Source: Sciurba et al. (2025).¹⁴

Sub-group analyses were not reported for the METREX mITT-300 population or the METREO mITT-300 population. The pooled mITT-300 population further studied the primary endpoint of annualised rate of moderate/severe exacerbations in up to ten subgroups and 28 subpopulations within those groups. Of these, ■ achieved statistical significance favouring mepolizumab over placebo. This analysis showed that no subgroup produced results that contradicted the overall trial findings, but some subgroup estimates were imprecise because small sample sizes led to wide confidence intervals.

Overall, the subgroup evidence across MATINEE, and the pooled mITT-300 population raises consistent concerns about reliability and interpretability. Many subgroup analyses were underpowered, and confidence intervals were often wide due to low participant numbers. Several analyses were post hoc (investigator-assessed COPD type and treatment required for exacerbations occurring during the study period) or done within already-restricted subgroups, increasing the risk of bias and undermining the protections of randomisation. The lack of multiplicity adjustment further limits the strength of any positive findings.⁸³ Furthermore, according to CONSORT guidelines for reporting of RCTs any secondary analyses should be pre-specified in the protocol, and if post-hoc analyses are being conducted this should be stated as strictly “hypothesis-generating” however, the Company has not provided that explanation on the subgroup analyses undertaken.⁷⁷ Together, these issues mean that the true pattern of treatment effects across subgroups remains uncertain, and the available analyses cannot confidently establish whether mepolizumab is consistently effective across different patient groups. The EAG recommends the interpretation of this information with caution and for these analyses to be taken as explorative.

3.4 Critique of studies identified and included in the indirect treatment comparison or multiple treatment comparison

Dupilumab for maintenance treatment of uncontrolled COPD with raised blood eosinophils [ID6235] guidance is currently in development (expected 11 February 2026).²⁴ Two additional trials (NOTUS and BOREAS) investigating the safety and efficacy of dupilumab, a comparator to mepolizumab listed in the NICE scope,³¹ are included in the ITC in the CS. Following PfC responses, the Company incorporated the results of these trials into a ML-NMA.¹² Both NOTUS (NCT04456673) and BOREAS (NCT03930732) were multi-centre, phase III, randomised, double-blind, placebo-controlled, parallel-group studies that evaluated the efficacy, safety and tolerability of dupilumab in patients with moderate to severe COPD with type 2 inflammation.^{63,84,85}

NOTUS was conducted between July 2020 and May 2024⁸⁴ and 935 eligible patients who were receiving triple inhaler therapy were randomised 1:1 to receive add-on SC dupilumab 300 mg (n=470) or matched placebo (n=465) every 2 weeks.⁶³ The trial had 329 sites in 29 countries (US, Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Czechia, France, Germany, Greece, Hungary, Latvia, Lithuania, Mexico, Netherlands, Peru, Poland, Portugal, Romania, Russia, Serbia, Slovakia, South Africa, Spain, Ukraine, UK).⁸⁴ It is unclear how many patients were drawn from the UK specifically.⁸⁴ While in BOREAS, conducted between April 2019 and May 2023, 939 patients were randomised 1:1 to receive either 300mg SC matched placebo (n=471). The trial was conducted across 275 sites in 24 countries not including the UK (Argentina, Bulgaria, Canada, Chile, China, Czechia, Denmark, Finland, Germany, Hungary, Israel, Italy, Japan, Mexico, Poland, Romania, Russia, Slovakia, South Korea, Spain, Sweden, Ukraine and the US).⁸⁵ A summary of the EAG's critique of the design and conduct of NOTUS and BOREAS is presented in Table 3:12.

Table 3:12: Summary of NOTUS and BOREAS methods critique

	BOREAS		NOTUS	
Trial design or conduct concept	Section in the CS where methods are reported	EAG's assessment	Section in the CS where methods are reported	EAG's assessment
Eligibility criteria	Bhatt et al. (protocol) ⁸⁶ Bhatt et al, 2023 (supplementary appendix) ⁸⁶	Appropriate All participants in BOREAS had to meet the following criteria: Age 40-80 years; current or former smokers with a history of ≥10 pack-years; moderate to severe COPD (post-bronchodilator FEV1 ≤70% and post-bronchodilator FEV1% predicted >30% and ≤70%); history of high exacerbation risk defined as ≥2 moderate or ≥1 severe within the year prior to inclusion; background triple therapy (ICS+LABA+LAMA) for 3 months prior to randomisation (double therapy: LABA + LAMA allowed if ICS is contraindicated); evidence of Type 2 inflammation (BEC ≥300 cells/μl). The EAG is satisfied that the inclusion criteria of BOREAS is broadly similar to the inclusion criteria of MATINEE, METREX and METREO.	Bhatt et al. (protocol) ⁶³	Appropriate All participants in NOTUS were receiving triple inhaler therapy (or LAMA/LABA if ICS was contradicted) and had a diagnosis of moderate to severe COPD. ⁶³ Prospective participants also had to be current or former smokers and had a documented history of high exacerbation risk (≥2 moderate or ≥1 severe). Evidence of Type 2 inflammation was also necessary - patients had to have BEC ≥300 cells/microliter at Visit 1 (Screening). These eligibility criteria are in line with the scope (aside from a diagnosis of moderate to severe COPD). The EAG are not unduly concerned about this (as it matches MATINEE, METREX and MATREO), and therefore, the EAG believes that the eligibility criteria are broadly appropriate.
Intervention	Bhatt et al, 2023. Protocol ⁸⁶	Appropriate	Bhatt et al. ⁶³	Appropriate

		Participants were randomised to receive dupilumab 300mg for SC administration every 14 days ($\pm$ 3 days). The EAG is satisfied that the intervention delivered in BOREAS was appropriate.	NOTUS clinical trial record ⁸⁴	Participants were randomised to receive add-on SC dupilumab at a dose of 300 mg every 2 weeks. ⁶³ This matches the recommended treatment dosage of dupilumab ⁸⁷ which was identified as a relevant comparator in the NICE scope. The technology is currently awaiting NICE approval (decision expected 11 February 2026). ²⁵ As such, the EAG considers dupilumab to be potentially appropriate, and an important comparator for this appraisal which guidance is still in development.
Comparator	Bhatt et al, 2023 Protocol ⁸⁶	Appropriate An identically matched placebo to dupilumab was given as a SC injection every 14 days ($\pm$ 3 days). The EAG is satisfied that placebo with SoC triple therapy (ICS + LABA + LAMA) is a suitable comparator and has no concerns.	Bhatt et al. ⁶³	Appropriate The placebo administered as one SC injection of placebo matching dupilumab was given as the comparator. Aside from dupilumab, triple therapy was also listed as a comparator in the NICE scope. The EAG regards placebo with standard care (triple therapy) as a suitable comparator and therefore have no concerns.
Randomisation	Bhatt et al. (protocol and (supplementary appendix) ⁸⁶ BOREAS clinical trial record ⁸⁵	Some concerns 936 participants were randomised in a 1:1 ratio to receive SC administrations of either dupilumab (n=468) or matching placebo for dupilumab (n=471). A centrally generated randomisation list was implemented via an IVRS/IWRS.	Bhatt et al. ⁶³ NOTUS clinical trial record ⁸⁴	Some concerns During the trial 935 participants were randomised from 329 sites in 29 countries in a 1:1 ratio to dupilumab (n=470) or placebo (n=465). Stratification was undertaken by country, the dose of inhaled

		Randomisation was stratified by country and by ICS dose (high ICS dose yes/no). Although the EAG is broadly satisfied with the method of randomisation, there are some concerns that stratifying by country can potentially create many strata. Please see Section 3.4.1 for further information.		glucocorticoid in use at baseline, and smoking status at the time of screening (enrolment of current smokers was capped at 30%). Although stratifying by country (and other factors) creates potentially many strata, the EAG are broadly happy with the randomisation method. See Section 3.4.1 for further information.
Allocation concealment	Bhatt et al. (trial protocol) ⁸⁶	Appropriate In BOREAS, participants were randomised using a permuted block randomisation schedule via interactive voice response system/interactive web response system (IVRS/IWRS) in a 1:1 randomisation ratio. The centralised treatment allocation system generated the patient randomisation list, according to which, IMPs were allocated to patients. Random permuted blocks as recommended by Cochrane RoB2, prevents predication of allocation.⁸⁸ Study medication (dupilumab or placebo) was provided in coded, identical and indistinguishable pre-filled syringes for SC injection to maintain allocation concealment. Overall, the EAG believes that the allocation concealment was appropriate, meeting recognised standards.	Bhatt et al. (trial protocol) ⁶³	Appropriate In NOTUS, patients were randomised using permuted-block randomisation, performed using an IVRS/IWRS. This allocation was not accessible to investigators or site staff at the time of patient enrolment, minimising the risk of selection bias. Study medication was supplied as coded, identical treatment kits, further maintaining concealment up to and beyond the point of randomisation. Random permuted blocks as recommended by Cochrane RoB2, prevents predication of allocation.⁸⁸ Overall, the EAG believe that the allocation concealment was appropriate, meeting recognised standards.

Blinding	Bhatt et al. (trial protocol) ⁸⁶	Appropriate In accordance with the double-blind design of BOREAS, study participants, investigators and study site personnel will remain blinded to study treatment and did not know which treatment had been assigned to each study participant. Unblinding was only permitted in the case of an AE, where knowledge of the investigational medicinal product (IMP) is required for treatment. The EAG considers the methods to ensure blinding in the BOREAS trial appropriate.	Bhatt et al. (trial protocol) ⁶³	Appropriate NOTUS was reported to be double-blinded; meaning that neither the patients, investigators (and study site personnel) knew which treatment each participant received during the study period. Unblinding was permitted only when knowledge of the investigational medicinal product was required for treating the patient. Although the protocol does not explicitly refer to outcome assessors, clinical and safety outcomes were assessed by blinded investigators and outcome assessment is therefore considered likely to have been blinded. Access to data with the potential to unblind the study was restricted, and interim analyses were conducted by independent statisticians separate from trial conduct. Overall, the EAG considers the blinding methods used in this trial to be appropriate.
Statistical analyses	Bhatt et al. (trial protocol) ⁸⁶	Appropriate The sample size of the BOREAS study was determined based on the primary endpoint (annualised rate of moderate or severe COPD exacerbations). It was assumed that the study had 90% power to detect a 25% relative risk reduction in the annualised rate of moderate or severe COPD exacerbations at the 2-	Bhatt et al. (manuscript and supplementary trial protocol) ⁶³	Appropriate The sample size was calculated based the primary endpoint (annualised rate of moderate or severe COPD exacerbations).⁶³ It was assumed that the study had a 90% power to detect a 25% relative risk reduction in the annualised rate of moderate or severe COPD exacerbations at the 2-tailed

		tailed significance level of $\alpha=0.05$. The primary endpoint was assessed in the ITT population, with safety analyses including all patients who received at least one dose of dupilumab (n=469) or placebo (n=470). The EAG considers the statistical analyses used to be appropriate.		significance level of $\alpha=0.05$.⁶³ The primary end point was assessed in the ITT population, with safety analyses including all patients who had received at least one dose of dupilumab (n=469) or placebo (n=464).⁶³ Accordingly, the EAG considers the statistical analyses appropriate.
Outcomes	Bhatt et al. (protocol)⁸⁶ Ct.gov record ⁸⁵	Appropriate The primary endpoint of the BOREAS trial was the annualised rate of acute moderate and severe COPD exacerbation. This was measured every 2 weeks including a 4-week screening period, a 52-week treatment period and a 12-week follow-up period. Secondary endpoints were: pre-bronchodilator forced FEV1 over 12 weeks compared to placebo; HRQOL assessed by change from baseline to Week 52 in the SGRQ; pre-bronchodilator FEV₁ over 52 weeks compared to placebo; lung function assessments; moderate to severe COPD exacerbations; safety and tolerability; and dupilumab systemic exposure and incidence of anti-drug antibodies. The EAG considers the outcomes assessed to be appropriate and relevant to the NICE scope.³¹	Trial protocol (supplementary appendix),⁶³ pp. 7-8.	Appropriate The primary endpoint was the annualised rate of moderate or severe COPD exacerbations over the 52-week treatment period compared to placebo.⁶³ Secondary endpoints included (i) change in pre-bronchodilator FEV1 from baseline to Week 12 compared to placebo; (ii) change from baseline to Week 52 in SGRQ total score compared to placebo; (iii) proportion of patients with SGRQ improvement ≥ 4 points at Week 52, and (iv) change in pre-bronchodilator FEV1 from baseline to Week 52 compared to placebo. The key outcome, related to exacerbation, was assessed and subsequently used for cost-effectiveness analysis. As this outcome was included in the NICE scope,³¹ the EAG consider the outcomes measured to be appropriate.

Subgroups	Bhatt et al. (protocol) ⁸⁶	Appropriate In BOREAS, subgroup analyses were conducted for the primary efficacy endpoints with respect to: age, gender, region, race, weight, BMI, smoking status, disease severity (as % post-bronchodilator FEV1), number of moderate-severe COPD exacerbation events within one year prior to the study, pre-bronchodilator FEV1, and other factors. The subgroup analysis specified in the NICE scope consisted of: levels of eosinophils (at least 500 cells per µl); severity of COPD; frequency of exacerbation within previous 12 months; CB or not; and smoking status.³¹ Although in BOREAS subgroup analysis for levels of eosinophils were not conducted, the EAG is satisfied that subgroup analysis conducted in BOREAS was appropriate.	Bhatt et al. (protocol)⁶³ Bhatt et al. (supplementary material)⁶³	Appropriate No subgroup analysis was specified in the NICE scope.³¹ However, pre-specified subgroup analyses were conducted for primary efficacy endpoint (annualised rate of moderate and severe COPD exacerbations over 52-week treatment period) with respect to age, gender, region, race, weight, BMI, smoking status, ICS dose, disease severity, number of moderate-or-severe COPD exacerbation events within one year prior to the study, pre-bronchodilator FEV1, and other factors. Baseline biomarker-by-treatment interaction on the efficacy endpoints was also analysed to evaluate the potential predictive effect of baseline biomarkers in the treatment response.⁶³ The EAG consider the range of subgroups to be appropriate.
Abbreviations: AE = Adverse events; BMI= Body Mass Index; CS = company submission; COPD = Chronic Obstructive Pulmonary Disease; CSR = clinical study report; EAG = External Assessment Group; FEV₁= Forced Expiratory Volume in 1 second; HRQOL= Health Related Quality of Life; ICS= Inhaled Corticosteroids; IMP= investigational medicinal product; ITT = Intention to Treat; RoB = Risk of Bias; SGRQ = St George's Respiratory Questionnaire. SC = subcutaneous; SoC = Standard of care;				

Table 3:13 Summary of EAGs interpretation of BOREAS and NOTUS trial results

Trial design or conduct concept	BOREAS		NOTUS	
Baseline characteristics	Bhatt 2023 (supplementary Appendix, Table S2) ⁸⁶	Appropriate Patient characteristics were similar across trial arms. The average age in the placebo group was 65.2 years and 65.0 years in the dupilumab group. For the placebo group, 84.3% of participants were White, 14.2% were Asian, in the dupilumab group this was 84% and 14.3%. The percentage of current smokers in the placebo groups was 31.4% and 28.6 in dupilumab group. No baseline characteristics were given for the number of pack-years. The mean screening eosinophil level was 532 cells/μL in the placebo group and 509 cells/μL in the dupilumab group. The EAG is satisfied that the baseline characteristics were similar between the placebo and dupilumab group, and similar compared to the METREO, METREX and MATINEE trials.	Bhatt et al.(manuscript and protocol) ⁶³	Appropriate Demographic and clinical characteristics were broadly comparable across trial arms. ‘White’ participants represented the largest ethnic grouping (ca. 89.5/89.9% across trial arms), with roughly 32% of participants of Hispanic or Latino ethnicity.⁶³ It is unclear how many patients were drawn from the UK. Participants also had to have blood eosinophil counts ≥ 300 cells/μL at Visit 1 (Screening), however at baseline approximately 40% of patients had < 300 cells/μL (balanced across treatment arms). Retesting of eosinophil values was allowed in the trial up to three times during the screening period to meet inclusion criteria for showing eosinophil count ≥ 300 cells/μL.⁶³ Clinical advice to the EAG indicates that blood eosinophil counts are indeed variable over time (with higher values with more severe disease/use of antibiotics, and lower values following the administration of steroids). While individual measurements may be variable, eosinophil counts obtained outside acute exacerbations would be most reflective of baseline status.

				Overall, the EAG considers the baseline characteristics to be consistent with those typically observed in UK clinical practice, and given the balanced treatment arms, no major concerns are identified.
Dropout rate	Bhatt 2023 (supplementary appendix) ⁸⁶ BOREAS clinical trial record ⁸⁵	Twenty-eight participants in the dupilumab group (6%) and 37 participants (8%) in the placebo group discontinued the study prior to Week 52. The EAG is satisfied with the overall retention rate, and that reasons for study discontinuation were broadly similar between the dupilumab and placebo group.	Bhatt et al. (supplementary appendix 1) ⁶³ NOTUS clinical trial record ⁸⁴	Appropriate Nineteen participants (5.2%) in the dupilumab arm and 22 (6.1%) participants in the placebo arm discontinued from the study prior to Week 52. The EAG is satisfied with the overall retention rate reported and acknowledge it was broadly similar across trial arms.
Outcomes:				
Lung function	Bhatt et al. 2023 ⁸⁶	Some concerns At Week 12, the least-squares mean difference in change from baseline in pre-bronchodilator FEV1 was 160ml 95% CI: 126 to 195) in the dupilumab group and 77ml (95% CI: 42 to 112). The least-squares mean difference was 83 ml (95% CI: 42 to 125); P<0.001). This improvement was observed within 2 weeks of initiation of dupilumab and sustained throughout up to week 52. At Week 52, the least-squares mean difference was	Bhatt et al. ⁶³	Some concerns At week 12, dupilumab improved FEV1 by 139 ml, compared with 57 ml for placebo (difference 82 ml, p<0.001). This benefit was maintained to week 52, though the difference was smaller (62 ml, p=0.02). Findings were consistent across subgroups and sensitivity analyses. In patients with baseline FeNO ≥20 ppb, the week-12 improvement was larger: 221 ml with dupilumab vs. 81 ml with placebo (difference 141 ml, p=0.001). However, by week 52 there was no significant difference. Although being in NICE scope for this appraisal, ³¹ lung function was not included in the MAIC. As such, lung function results for dupilumab compared to mepolizumab cannot

		83ml (95% CI: 38 to 128, P<0.001). Although being in NICE scope for this appraisal, lung function was not included in the MAIC, as such lung function results for dupilumab compared to mepolizumab cannot be quantified, and there remains considerable uncertainty.		be quantified and there remains considerable uncertainty.
Frequency of moderate or severe exacerbations	Bhatt 2023, Supplementary Appendix, Table S3. ⁸⁶	Appropriate The annualised rate of moderate or severe COPD exacerbations was 0.78 (95% CI: 0.64 to 0.93) versus 1.10 (95% CI: 0.93 to 1.30). The RR vs placebo was 0.704 (95% CI: 0.581 to 0.852). Since these outcomes were included in the MAIC, the EAG considers these outcomes to be appropriate.	Bhatt et al. ⁶³	Appropriate The annualised rate of moderate or severe exacerbations of COPD was lower in the dupilumab group (0.86; 95% CI, 0.70 to 1.06) than in the placebo group (1.30; 95% CI, 1.05 to 1.60), resulting in a rate ratio of 0.66 (95% CI, 0.54 to 0.82; P<0.001). The time to first moderate/severe exacerbation was also included as a secondary outcome (HR 0.71; 95% CI, 0.57 to 0.89). Since these important outcomes were included in the ITC, the EAG considers these outcomes appropriate.
Frequency of exacerbations resulting in hospital admission or ED visit	N/A	Outcome not assessed	Bhatt et al. ⁶³	Appropriate In NOTUS, the annualised event rate of severe COPD exacerbation was included as a secondary outcome. Severe exacerbations (per participant year) were lower in the intervention arm (0.070, 95% CI 0.039 to 0.123) compared to the control (0.124, 95% CI 0.072 to 0.215), highlighting the relationship was statistically significant. The annualised rate of severe exacerbations was used in the

				ITC and therefore the EAG find this approach appropriate.
Symptom control	Bhatt 2023 ⁸⁶	Appropriate Improvement from baseline in the SGRQ total score at week 52 was greater in the dupilumab group compared to the placebo group. The least-squares change in SGRC total score from baseline to week 52 mean was -6.4 (95% CI: -8.0 to -4.8) in the placebo group compared to -9.7 95% CI: (-11.3 to -8.1). The least-squares mean difference versus placebo was -3.4 (95% CI: -5.5 to -1.3). The percentage of patients who had ≥ 4 points improvement in Week 52 in SGRQ total score was 51.5% (95% CI: 46.9 to 56.1) in dupilumab group and 43.1% (95% CI: 38.6 to 47.7) in the placebo group. The OR versus placebo was 1.4 (95% CI: 1.1 to 1.9). Both the change from baseline for SGRQ-C total score at week 52 and the SGRQ-C total score response at week 52 were both included in the ITC. Therefore, the EAG considers this appropriate.	Bhatt et al. ⁶³	Appropriate At week 52, patients receiving dupilumab showed a greater improvement in SGRQ total score than those on placebo (-9.8 vs. -6.4 points), resulting in a least-squares mean difference of -3.4 points. Around half of patients in both groups achieved the minimum clinically important improvement of ≥ 4 points (51.4% with dupilumab vs. 46.5% with placebo). Changes in E-RS-COPD total scores were modest and similar between groups, with a slight numerical advantage for dupilumab (-2.4 vs -1.8 points), but the between-group difference (-0.6 points) did not clearly favour either treatment. The change from baseline for SGRQ-C total score at week 52 and the SQGQ-C total score response at week 52 were both used in the ITC and therefore the EAG find this approach appropriate.

Mortality	Bhatt 2023 (supplementary appendix), Table S9 ⁸⁶	Some Concerns Cardiovascular death occurred in 0.6% of participants in the placebo group and 0.2% of participants in the dupilumab group. Although being in the NICE scope for this appraisal, mortality was not included in the MAIC. As such, mortality results for dupilumab compared to mepolizumab cannot be quantified and there remains uncertainty.	Bhatt et al. ⁶³	Some concerns All-cause mortality was higher in the dupilumab arm (14/469 patients; 2.99%) compared to the control arm (8/464 patients, 1.72%). Although being in NICE scope for this appraisal, mortality was not included in the MAIC. As such, mortality results for dupilumab compared to mepolizumab cannot be quantified and there remains uncertainty.
Adverse effects of treatment	Bhatt 2023, Table 3 ⁸⁶	Some concerns AEs were similar between the dupilumab group and placebo group. Any AEs and SAEs occurred in 76% and 16% respectively of participants in the placebo group, this was compared to any AE leading to death occurred in 1.7% of participants in the placebo group and 1.5% of participants in the dupilumab group. Any AEs leading to permanent discontinuation was 3.4% in the placebo group and 3% in the dupilumab group. The most common AEs in both groups were nasopharyngitis, upper respiratory tract infection,	Bhatt et al. ⁶³	Some concerns Any AEs and SAEs occurred in 65.9% and 66.7% of patients treated with placebo and dupilumab respectively. Any AE leading to death occurred in 1.5% of patients in placebo vs. 2.6% in the dupilumab arm. 2.6% (placebo) and 3.8% (dupilumab) of patients in each arm had AEs that led to discontinuation. The most common AEs was COVID-19, COPD and nasopharyngitis. The EAG consider that the safety profile presented is acceptable, however AEs were not compared between dupilumab and mepolizumab.

		headache, diarrhoea, back pain, COVID-19 and hypertension. The EAG is satisfied that AEs were similar between both groups and the safety profile was acceptable. However, AEs were not compared between dupilumab and mepolizumab.		
Subgroup analysis	Bhatt 2023, Supplementary appendix, Figures S3 and S4 ⁸⁶	Appropriate The RRs in the annualised rate of moderate or severe COPD exacerbation favoured dupilumab versus placebo across all of the prespecified subgroup analyses, providing evidence for an overall benefit of dupilumab versus placebo. However, the small sample size of the subgroups reduces the power of analyses and therefore warrants caution in interpretation.	Figures S3 and S4, Bhatt et al. ⁶³	Appropriate The RRs in the annualised rate of moderate or severe COPD exacerbation consistently favoured dupilumab versus placebo across all prespecified patient subgroups. Although the analyses provide supportive evidence for an overall benefit of dupilumab over placebo regardless of the covariates tested, the small sample sizes of these subgroups reduce the power of these analyses and therefore warrants caution in their interpretation.
Abbreviations: AE = adverse event; CI = confidence interval; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; EAG = External Assessment Group; E-RS-COPD = Evaluating Respiratory Symptoms in COPD; FEV ₁ = forced expiratory volume in 1 second; FeNO = fractional exhaled nitric oxide; HR = hazard ratio; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; mL = millilitre; ppb = parts per billion; RR = rate ratio; SAE = serious adverse event; SGRQ = St George's Respiratory Questionnaire; SGRQ-C = St George's Respiratory Questionnaire for COPD; uL = microlitre.				

3.4.1 Randomisation

The prevalence of COPD, including exacerbations, varies geographically due to differences in environmental exposures (e.g. smoking history, air pollution, and exposure to smoke from biomass fuels).^{89,90} The EAG therefore agrees that stratification by country may help to reduce confounding. However, both dupilumab trials included many participating countries (24 in NOTUS and 29 in BOREAS), raising concerns about the number of participants allocated to each stratum. As neither trial publicly reports the number of patients enrolled by country, there is uncertainty regarding the appropriateness of this stratification approach. Consequently, the EAG has concerns regarding the robustness of the analysis.

3.4.2 Lung function, mortality and adverse effects of treatment

These outcomes were included in the NOTUS trial but were not included in the ITC analyses for this appraisal. Only the primary outcome of frequency of moderate or severe exacerbations was included in the ML-NMR following the response to Pfc.¹² The EAG agree with the Company that frequency of moderate and/or severe exacerbations is the most important outcome, as it is the key driver of disease burden, healthcare resource use, costs, and health-related quality of life, and therefore the most relevant outcome. Since exacerbations are the key input for cost-effective modelling, the EAG are not overly concerned that lung function, mortality and adverse effects of treatment are not compared between treatment with mepolizumab and dupilumab.

3.5 Critique of the Indirect Treatment Comparisons (ITCs)

No direct evidence was available to compare mepolizumab with dupilumab for COPD patients with an eosinophilic phenotype. The Company's SLR identified two RCTs (BOREAS⁸⁵ and NOTUS⁸⁴) that provide evidence for dupilumab in patients with COPD and blood eosinophil levels ≥ 300 cells/ μ L.

IPD were available for mepolizumab, whereas only aggregate data were available for dupilumab. The Company undertook Bucher ITCs and MAICs which indirectly compared mepolizumab with dupilumab considering placebo as the common comparator. The Bucher ITC method uses aggregate data for both drugs (mepolizumab and dupilumab) and assumes the populations across trials are similar in relation to the distribution of effect modifiers. Consequently, it does not adjust for effect modifiers. The MAIC approach combines published aggregate data for the comparator drug (dupilumab) with IPD for the drug of interest (mepolizumab). It adjusts for cross-trial differences in effect modifiers by aligning the IPD to the aggregate baseline characteristics of the comparator trial. Hence, the Bucher ITC method provides unadjusted effect estimates whereas MAICs enable standardisation of effect modifiers across trials. Reporting the results from both analyses shows whether population differences significantly impact treatment effect estimates. Where results are similar, this increases confidence in the findings. In addition to the Bucher ITCs and MAICs, the EAG also asked the Company to perform ML-NMR analyses to compare the effectiveness of mepolizumab versus dupilumab.¹² This approach allows adjustment for effect modifiers by including them as covariates in the statistical model, without reducing the effective sample size as occurs with MAICs due to the matching process. As a result, it enhances the statistical power of the analysis and improves the precision of the estimated effects.⁵⁰ The Company provided the results of the ML-NMR analysis for the primary endpoint, namely annualised rate of moderate/severe exacerbations, adjusted for the same variables as the MAICs.¹² A homogeneous patient population was achieved across the mepolizumab and dupilumab trials for the ITCs by excluding patients from the mepolizumab trials who did not meet the eligibility criteria for the dupilumab trials; specifically, patients without CB, those with BEC <300 cells/ μ L at screening, mMRC <2, or post-bronchodilator FEV1 outside the moderate-severe range (i.e., GOLD 4 or mild disease). All analyses were conducted using the two definitions of CB applied in the dupilumab trials: one based on investigator assessment (drawing on data from MATINEE, BOREAS and

NOTUS that used this definition), and the other based on responses to the SGRQ (using data from MATINEE, METREX and METREO; BOREAS and NOTUS, all of which applied this definition). A summary of the critique of the ITC methods used by the Company is reported in Table 3:14.

Table 3:14: Summary of the EAG's critique of the Company's ITCs

Aspect of ITC design or conduct	Bucher ITC		MAIC		ML-NMR	
	Section in the CS where methods are reported	EAG's assessment	Section in the CS where methods are reported	EAG's assessment	Section in the CS where methods are reported	EAG's assessment
Statistical methods	CS, Section 2.10 ⁶	Appropriate The EAG considers the Bucher ITC is an appropriate method for providing unadjusted effect estimates comparing the effectiveness of mepolizumab versus dupilumab.	CS, Section 2.10 ⁶	Some concerns The EAG considers the MAIC to be an appropriate method for comparing the effectiveness of mepolizumab and dupilumab whilst adjusting for effect modifiers. The loss of effective sample size is a limitation of this approach; however, the EAG is satisfied that this is addressed by the ML-NMR analyses, for the primary outcome. The EAG has some concerns that the Company did not provide sufficient evidence that all the	PfC response ¹²	Some concerns The EAG considers the ML-NMR to be an appropriate method for comparing the effectiveness of mepolizumab and dupilumab whilst controlling for effect modifiers as covariates and whilst retaining the effective sample size, thereby increasing precision and power of the results compared to MAIC analyses. The EAG has some concerns that the Company did not provide sufficient evidence that all variables adjusted for were effect modifiers.

Aspect of ITC design or conduct	Bucher ITC		MAIC		ML-NMR	
	Section in the CS where methods are reported	EAG's assessment	Section in the CS where methods are reported	EAG's assessment	Section in the CS where methods are reported	EAG's assessment
				variables adjusted for were effect modifiers. Please see Section 3.5.1 for further comment.		Please see Section 3.5.1 for further comment.
Included and excluded studies	CS, Section 2.10 ⁶	Appropriate The EAG notes that the Company did not provide a feasibility assessment for the ITC analyses. However, it considers the studies that were included appropriate for the indirect comparisons. Furthermore, the EAG did not identify any additional studies that should have been included in the ITCs.	CS, Section 2.10 ⁶	Appropriate Same critique as for Bucher ITC.	CS, Section 2.10 ⁶	Appropriate Same critique as for Bucher ITC.
Transitivity (study characteristics)	CS, Section 2.10, Tables 33-34 ⁶	Secondary Issue 4 Baseline characteristics were reasonably well balanced between groups. $\geq 5\%$ differences were observed between groups	CS, Section 2.10, Tables 33-34 ⁶	Secondary Issue 4 Same critique as for Bucher ITC. Please see Section 3.5.2 - Transitivity for further comment.	CS, Section 2.10, Tables 33-34 ⁶	Secondary Issue 4 Same critique as for Bucher ITC. Please see Section 3.5.2 - Transitivity for further comment.

Aspect of ITC design or conduct	Bucher ITC		MAIC		ML-NMR	
	Section in the CS where methods are reported	EAG's assessment	Section in the CS where methods are reported	EAG's assessment	Section in the CS where methods are reported	EAG's assessment
		for some variables (BMI, Region, Severe exacerbations at baseline and SGRQ-C), however, these variables were adjusted for in the MAIC and ML-NMR analyses. Clinical advice to the EAG suggested that baseline characteristics across the trials were broadly representative of the population of interest in UK clinical practice. SoC was not completely standardised between participants in the mepolizumab trials (who were all receiving optimised, triple therapy) and those in the dupilumab trials (some of whom were contraindicated to ICS, were receiving dual				

Aspect of ITC design or conduct	Bucher ITC		MAIC		ML-NMR	
	Section in the CS where methods are reported	EAG's assessment	Section in the CS where methods are reported	EAG's assessment	Section in the CS where methods are reported	EAG's assessment
		therapy). However, nearly all patients in the dupilumab trials were receiving triple therapy.⁶³ The EAG does not consider that this was likely to impact significantly on the results. The EAG has some concerns that both dupilumab trials were conducted during the Covid pandemic, whereas only one of the mepolizumab trials (M ATINEE) was conducted during the same period (METREX and METREO were conducted pre-Covid). Please see Section 3.5.2 and Section 1.4 for further comment.				
Results	CS, Section 2.10 ⁶	Some concerns The Company did not report ITC analyses for the safety	CS, Section 2.10 ⁶	Some concerns Same critique as for Bucher ITC.	CS, Section 2.10 ⁶	Some concerns Same critique as for Bucher ITC.

Aspect of ITC design or conduct	Bucher ITC		MAIC		ML-NMR	
	Section in the CS where methods are reported	EAG's assessment	Section in the CS where methods are reported	EAG's assessment	Section in the CS where methods are reported	EAG's assessment
	██████████ PfC response¹²	outcomes. They justified this based on comparability in safety outcomes between the mepolizumab/ dupilumab and placebo groups in the clinical trials. The EAG considers this approach to be appropriate. The direction of effect for the primary endpoint is inconsistent with the MAIC and ML-NMR. Please see Section 3.5.3 for further details.	PfC response¹²	The direction of effect for the primary endpoint is consistent with the ML-NMR but is inconsistent with the Bucher ITC. The EAG could not assess whether the proportional hazards assumption holds for the comparison between mepolizumab and dupilumab. The Company provided evidence of proportionality for mepolizumab vs placebo but not when comparing the drugs. Please see Section 3.5.3 for further details.	PfC response¹²	The Company conducted this analysis for the primary endpoint only, however, the EAG are satisfied with this approach given the limited time available for the Company to provide the additional analyses. The direction of effect for the primary endpoint is consistent with the MAIC but inconsistent with the Bucher ITC, although the results from both analyses cross the line of no effect. Please see Section 3.5.3 for further details.

Bucher ITC			MAIC		ML-NMR	
Aspect of ITC design or conduct	Section in the CS where methods are reported	EAG’s assessment	Section in the CS where methods are reported	EAG’s assessment	Section in the CS where methods are reported	EAG’s assessment
Sensitivity analyses	CS, Section 2.10, Table 35 ⁶	Appropriate All analyses were conducted using the two definitions of CB applied in the dupilumab trials: one based on investigator and the other based on responses to the SGRQ-C both at baseline. The EAG considers this appropriate and notes that the results are consistent in both analyses.	CS, Section 2.10, Table 35 ⁶	Some concerns All analyses were conducted using the two definitions of CB applied in the dupilumab trials: one based on investigator and the other based on responses to the SGRQ-C both at baseline. The EAG considers this appropriate, however, it notes that the direction of effect favours mepolizumab in one of the analyses and dupilumab in the other. Please see Section 3.5.3 for further details.	PfC response ¹²	Some concerns All analyses were conducted using the two definitions of CB applied in the dupilumab trials: one based on investigator and the other based on responses to the SGRQ-C both at baseline. The EAG considers this appropriate, however, it notes that the 95% CI is wider for the analysis based on investigator-assessed CB than for CB based on SGRQ-C scores. Please see Section 3.5.3 for further details.

Abbreviations:; CS = company submission; EAG = External Assessment Group; ITC = indirect treatment comparison; MAIC = matched-adjusted indirect comparison; ML-NMR= multi-level network meta-regression; SGRQ-C = St George’s Respiratory Questionnaire – COPD-specific version

3.5.1 Statistical analysis

The Company conducted ITC methods using a frequentist approach, whereby effective sample size was computed as the square of the summed weights divided by the sum of the squared weights (CS Section 2.10.4, pg. 111-112).⁶ Additional analyses was requested and conducted on the primary outcome, using a Bayesian analysis; ML-NMR. The Company used uninformative priors, which means the results should be comparable to the frequentist analysis.

In the MAIC analyses, the Company adjusted for a range of variables (such as age, sex, smoking status, BEC, prior exacerbation history, and quality of life scores) that were considered as potential '*confounders/effect modifiers*'. The Company did not initially provide rationale for adjusting for these variables in the original CS⁶ and the EAG sought clarification. The Company stated the variables were selected based on baseline characteristics from published clinical trials of both mepolizumab and dupilumab. Additionally, an internal pulmonologist was consulted. The same variables were included in the ML-NMRs as covariates.¹² Clinical advice to the EAG indicates that baseline BEC at screening—one of the variables adjusted for in the MAICs and included as a covariate in the ML-NMR analyses—is likely to be an effect modifier, as evidence from the clinical trials suggests that higher baseline BEC is associated with a greater treatment effect. The EAG consulted the clinical expert who also suggested that smoking status and corticosteroid treatment may be effect modifiers. In contrast, the remaining variables adjusted for in these analyses could be purely prognostic factors, meaning they influence outcomes but do not modify treatment effects. Adjusting for such prognostic variables is not recommended, as doing so can increase the standard error due to over-matching.⁹¹ Furthermore, some variables not included as covariates could be potential effect modifiers. For example, the clinical advisor stated that one of the subgroup analyses, mMRC score, has the potential to be an effect modifier.

3.5.2 Transitivity

The ITCs incorporated five clinical trials. Three of these—one trial of mepolizumab (MATINEE) and two trials of dupilumab (NOTUS and BOREAS)—were conducted during the Covid-19 pandemic, whereas the remaining two mepolizumab trials (METREX and METREO) were conducted prior to the pandemic (see Section 3:15). Differences in trial timing may affect comparability of treatment effectiveness, as COPD exacerbation rates were substantially lower during the pandemic.¹¹ This could make dupilumab appear less effective than mepolizumab, as the reduced number of exacerbations limits the ability of treatments to demonstrate an effect on exacerbation outcomes.

To address this issue, the EAG suggests that the Company conduct sensitivity analyses using only the 52-week follow-up data from the MATINEE, BOREAS and NOTUS trials, which were carried out during the Covid-19 pandemic. This is a Secondary Issue (Secondary Issue 4; see Section 1.4).

Table 3:15: Summary of participant numbers and study dates for trials included in the ITC analyses (before matching).

	Mepolizumab trials			Dupilumab trials	
	MATINEE	METREO	METREX	NOTUS	BOREAS
NCT number	NCT04133909	NCT02105948	NCT02105961	NCT04456673	NCT03930732
mITT population ^a	804	449	836	1,874	
Number of patients analysed (N) (defining CB based on investigator assessment in MATINEE trial) ^{a,b}	■	NA	NA	1,874	
Number of patients analysed (N) (defining CB based on SGRQ-C responses at baseline in mepolizumab trials) ^{a,b}	■	■	■	1,874	
Study start	October 2019 ^c	April 2014 ¹⁵	April 2014 ¹⁵	July 2020 ^c	April 2019
Primary completion	August 2024 ^c	January 2017 ¹⁵	January 2017 ¹⁵	May 2024 ^c	May 2023
Impacted by COVID?	Yes	No	No	Yes	Yes
^a Both placebo and mepolizumab/dupilumab treatment arms included. The mepolizumab 300 mg dose is not included in the restricted population from METREX. ⁶ ^b Number of participants from each study that were included in the ITC analyses (restricted population from METREX and METREO after the applying the eligibility criteria in BOREAS/NOTUS trials) based on different definitions of CB. Participant numbers were derived from CS Section 2.10.7 Tables 32-33 ⁶ ; ^c Study start and completion dates obtained from the clinical trial registrations clinical trials.gov ^{65,84} as these were not available in the key trial publications Abbreviations: CB = Chronic Bronchitis; mITT = modified intention to treat; NA = not applicable; SGRQ-C = St. George's Respiratory Questionnaire – COPD specific version.					

3.5.3 Results and sensitivity analyses

The EAG requested the Company undertook ML-NMR analyses to allow for the inclusion of all patients in the analysis and therefore negate the impact on the effective sample size (ESS). This was possible, within the timeframe, for the primary outcome of annualised exacerbations. For population 1 (where CB was defined based on investigator assessment), the magnitude and direction of effect for the primary endpoint (annualised rate of moderate/severe exacerbations) was similar from the (adjusted) MAIC⁶ and ML-NMR analyses¹² - both of which favoured mepolizumab based on the direction of effect. However, the direction of effect favoured dupilumab in the (unadjusted) Bucher ITC analyses:^{6,12}

- ML-NMR results: rate ratio ([REDACTED])
- MAIC results: RR 0.91, 95% CI 0.60 to 1.37
- Bucher ITC results: RR 1.09, 95% CI 0.78 to 1.53

The use of the ML-NMR negates the reduction in effective sample size, which means the whole cohort of patients can be included in the analyses. However, in some situations, we may see an increase in uncertainty (wider CrIs/CIs). In the current example, in which the Company also noted that the 95% CrI is wider from the ML-NMR compared to the CI of the MAIC analyses,¹² this increased imprecision is likely due to population heterogeneity which was not included in the MAIC due to the matching process. The MAIC included ([REDACTED]) of ([REDACTED]) patients from the mepolizumab arm and ([REDACTED]) of ([REDACTED]) patients from the placebo arms of the MATINEE trial.⁶ The ML-NMR allowed for the inclusion of all patients.

For population 2 (where CB was defined based on SGRQ-C responses at baseline), the results based on direction of effect were comparable across all the analyses and favoured dupilumab:^{6,12}

- ML-NMR results: [REDACTED]
- MAIC results: RR 1.13, 95% CI 0.80 to 1.58

- Bucher ITC results: RR 1.09, 95% CI 0.84 to 1.41

The EAG notes that the 95% Crls for the ML-NMR result is narrower for population 2 than for population 1, which is likely to reflect the increased larger effective sample size following matching in population 2.

As the 95% CrIs/CIs cross the line of no effect for the primary and other outcomes assessed, the EAG concludes that the results suggest that mepolizumab and dupilumab have similar effectiveness profiles. The MAIC included (■■■) of (■■■) patients from the mepolizumab arm and (■■■) of (■■■) patients in the placebo arm.⁶ The ML-NMR allowed for the inclusion of all patients.

For the secondary outcome of the time to first exacerbation, the EAG requested evidence of the proportionality assumption holding and sensitivity analyses. In the response to points for clarification (question A3) the Company provided Kaplan-Meier curves, log-cumulative hazard plots and Schoenfeld residual plots for mepolizumab compared to placebo.¹² The Company suggest that the plots show proportionality is maintained for both population 1 and 2 analyses. In the population 1 analysis, the EAG do note a potential cross over in the beginning of the trial for mepolizumab vs placebo in population 1, in the Kaplan-Meier curve. The Company also note in the log-cumulative plot a cross over early in the trial. This is likely driven by few events occurring. The EAG therefore agree that the proportional hazard assumption likely holds, especially given the widening of the two arms over time. No such crossover is noted in population 2 and therefore, there are no concerns for this model either. The Company conducted proportional hazard models using the Gompertz, Weibull and Exponential models.¹²

For population 1 the results for mepolizumab compared to placebo were similar:¹²

- Cox results: [REDACTED] Weibull results:

- Exponential results: [REDACTED]
- Gompertz results: [REDACTED]

For population 2 the results for mepolizumab compared to placebo were similar.¹²

- Cox results: [REDACTED]
- Weibull results: [REDACTED]
- Exponential results: [REDACTED]
- Gompertz results: [REDACTED]

The EAG therefore consider the results of the Cox proportional hazards analysis to be robust when comparing to the placebo. However, no evidence was provided of the proportional hazards assumption holding for the comparison between mepolizumab and dupilumab. Therefore, the EAG could not assess whether this was the most appropriate analysis or not (Secondary Issue 5; see Section 1.4).

For the HRQoL outcomes, change from baseline for SGRQ-C total score at Week 52 favoured dupilumab based on the direction of effect for all analyses.⁶ None of these differences were statistically significant:

Population 1:

- MAIC results: Mean difference (MD) 1.04, 95% CI -2.62 to 4.69
- Bucher ITC results: MD 1.34, 95% CI -2.62 to 5.3

Population 2:

- MAIC results: MD 1.70, 95% CI -1.46 to 4.86
- Bucher ITC results: MD 1.42, 95% CI -1.88 to 4.71

The results for SGRQ-C total score response at Week 52 favoured dupilumab based on the direction of effect for all analyses apart from the MAIC for Population 1.⁶ None of these results were statistically significant:

Population 1:

- MAIC results: RR 1.19, 95% CI 0.63 to 2.24
- Bucher ITC results: RR 0.88, 95% CI 0.53 to 1.45

Population 2:

- MAIC results: RR 0.96, 95% CI 0.58 to 1.58
- Bucher ITC results: RR 0.97, 95% CI 0.65 to 1.46

3.6 Additional work on clinical effectiveness done by the EAG

No additional work surrounding clinical effectiveness was undertaken by the EAG.

3.7 Conclusions of the clinical-effectiveness Section

3.7.1 Conclusions of the clinical effectiveness SLR

The methods of the SLR were in the main considered appropriate by the EAG. However the EAG raise the issue of whether selection bias may have been introduced as two studies which either: did not fully meet the eligibility criteria, IMPACT;⁹ or were not identified by the SLR, ECLIPSE,¹⁰ were used to generate a pooled population to inform the baseline patient characteristics and impact of standard of care on HRQoL in the economic model. This may also underestimate the baseline utilities and disutilities (see Section 1.4, Secondary Issue 3 and Sections 3.1.4 and 3.1.5 for further information).

3.7.2 Conclusions on the MATINEE, METREX and METREO trials

Three key trials were included in the CS, MATINEE, METREO and METREX; efficacy data for the mITT-300 population from all three trials were analysed in a pooled analysis. The EAG's critique of the methods and results of these are summarised in Sections 3.2 and 3.3. All three trials are international, randomised, double-blind trials, with MATINEE being the main phase III trial and the phase III METREO and METREX trials providing supportive data. The EAG identified no Key Issues with the trials. However, some Secondary Issues and Some Concerns were raised in relation to several aspects of the methods and results, which are summarised below.

It was unclear what proportion of patients in the mepolizumab trials had received the 'five fundamentals of COPD care', namely: smoking cessation; vaccinations (pneumococcal and influenza), pulmonary rehabilitation if indicated, co-development of a personalised self-management plan and optimised identification and treatment for comorbidities.¹ Clinical advice to the EAG and evidence from patient groups suggests that only a small proportion of patients receive all 5 standards of care. ^{2,3} If all COPD patients received the 'five fundamentals of COPD care' it is likely that patients would have reduced exacerbations (in terms of severity and frequency) and that the benefit from mepolizumab would likely be smaller. This has been identified by the EAG as a Secondary Issue (Secondary Issue 1; Section 1.4).

The EAG identified the inclusion of a subset of patients from the METREX and METREO trials in the mITT-300 pooled analysis as a Secondary Issue (Secondary Issue 6; Section 1.4). This is because the selection of a patient subset undermines the randomisation process, meaning that the balance of prognostic factors may not be equally balanced between groups in the pooled analysis. The EAG did not identify notable imbalances between the primary studies and the pooled analysis in relation to the baseline characteristics reported by the Company (CS Table 9).⁶ Also, clinical advice to the EAG confirmed that patients in the pooled analysis were representative of those

seen in clinical practice in the UK (apart from ethnic profile, which was not considered a prognostic factor). However, this does not ensure comparability of participants in each of the trial arms in the pooled analysis as unreported prognostic factors may have differed.

In relation to the methods used in the MATINEE, METREO and METREX clinical trials, a Secondary Issue was identified in relation to the eligibility criteria. This was due to the fact that key comorbidities, such as diabetes or cardiac diseases, are common in real-world COPD populations.¹³ However, in the three pivotal trials for mepolizumab (MATINEE, METREX and METRE), patients were excluded if they presented with unstable or life-threatening cardiac disease or presented with historic or current clinically significant neurological, psychiatric, renal, hepatic, immunological, endocrine or haematological abnormalities that were uncontrolled,^{14,15} While clinically justified this limits the external validity of the evidence and introduces uncertainty regarding the generalisability of the observed treatment effects to the broader UK COPD population who are likely to receive mepolizumab in routine practice. The EAG has identified this as a Secondary Issue (Secondary Issue 7; see Section 1.4). Also regarding the eligibility criteria, Some Concerns were identified by the EAG in relation to the fact that the population specified in the Company decision problem is narrower than the NICE scope; however, clinical advice to the EAG suggested that the eligibility criteria used in the MATINEE, METREO and METREX clinical trials were appropriate. Analyses of the primary endpoint (and additional analyses) appear to have been underpowered in METREX and METREO, where the mITT-300 population was analysed as a subgroup. In contrast, MATINEE defined the mITT population using a BEC threshold applied to all participants, and statistical power for the primary endpoint was achieved for the mITT-300 population in this trial. Also, the issue of power was addressed by the mITT-300 pooled analysis for the efficacy outcomes.

Regarding the results, the EAG identified some concerns in the following areas: baseline characteristics, drop-out rate, exacerbation and HRQOL outcomes. Regarding the baseline characteristics, some imbalances (>5%)

between groups were identified for sex, smoking status and mMRC score. However, the EAG does not believe that these imbalances are necessarily incompatible with chance. Additionally, the distribution of different SoC regimens and the receipt of the five COPD fundamentals recommended by NICE (smoking cessation support, pneumococcal and influenza vaccinations, a personalised self-management plan, pulmonary rehabilitation and optimal treatment for comorbidities) was not reported for each group. These could act as effect modifiers. However, the randomisation process may have equally distributed these interventions between the trial arms in each study. The study withdrawal and treatment discontinuation rates were generally acceptably low; however, the rates were generally higher in the placebo compared to the mepolizumab 100mg groups. Attrition bias may have been introduced if the proportions of patients with effect modifying characteristics were imbalanced between groups at the follow up time points. For the primary and secondary exacerbation endpoints, the MATINEE trial showed increased efficacy for the 104 follow up time point compared to the 52-week time point, which could reflect that participants who continued their treatment to 104 weeks were clinically fitter, more adherent, or early responders. Other possible explanations include a cumulative benefit of using mepolizumab 100mg for a longer duration, and the increased rate of exacerbations that occurred after the Covid pandemic which provided more opportunity for the effects of mepolizumab compared to placebo to become apparent. The lack of CMID thresholds for the exacerbation outcomes is an issue that was raised in the appraisal of dupilumab for eosinophilic COPD and will not be re-addressed here.²⁴ None of the HRQOL outcomes showed significant improvements following mepolizumab 100mg treatment. This may reflect imprecision in the analyses, a generally poor quality of life in the eosinophilic COPD population and/ or the less objective and less tangible nature of self-assessed quality of life assessments compared to other health outcomes. None of these points were identified by the EAG as being key issues; however, they are important to note.

3.7.3 Conclusions on the ITCs

The EAG considers that the methodological approach taken by the Company to conduct the ITC analyses were broadly appropriate. Some concerns that were identified, included matching/ controlling for factors which clinical advice to the EAG suggested were purely prognostic rather than effect modifiers; this may have reduced the precision of the analyses. The EAG also noted differences in the direction of effect between adjusted versus un-adjusted analyses and in relation the definition of CB that was used to select data for the analyses; however, none of the results were significantly different, indicating comparability between mepolizumab and dupilumab. The Company did not provide evidence for the assessment of the proportionality assumption between the mepolizumab and dupilumab, which are analysed using Cox proportional hazards in the MAIC for the secondary outcome of time-to-first moderate/severe exacerbation. If this assumption is not met sufficiently, the underlying assumption of the Cox analysis is threatened, a non-proportional hazards method may be preferred. The EAG identified this as a Secondary Issue (Secondary Issue 5; see Section 1.4). Finally, both dupilumab trials but only one out of three mepolizumab trials were undertaken during the covid pandemic, when COPD exacerbations were significantly less frequent and the drugs had less potential to demonstrate their effectiveness. This could have inflated the effectiveness of mepolizumab compared to dupilumab; therefore, this was identified as a Secondary Issue (Secondary Issue 4; Section 1.4) and the EAG suggested that the Company perform sensitivity analyses including data that was collected during the Covid pandemic (MATINEE, BOREAS and NOTUS 52 week follow up data).

4 Cost effectiveness

This Section presents a summary and critique of the cost-effectiveness evidence included in the CS. Section 4.1 focuses on the Company's review of the cost-effectiveness evidence and Section 4.2 covers the Company's economic evaluation.

4.1 Critique of the review of cost-effectiveness evidence

The Company conducted an SLR to identify evidence on the cost-effectiveness, healthcare resource use (HCRU) and costs associated with patients with moderate, severe, or very severe COPD receiving treatment with triple therapy (ICS/LABA+LAMA) or dual therapy with add on therapies (see CS Appendix E⁹² and G⁹³ respectively). Additionally, an SLR was conducted to identify HRQoL/utility data in patients with moderate to very severe COPD (see CS Appendix F⁹⁴). The Company reported their methodological approaches and the results of their original SLRs conducted in October 2016, which were subsequently updated in May 2018, July 2024, and September 2025. Each SLR were stated by the Company^{92,94} as conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards⁵⁷ and the Centre for Reviews and Dissemination (CRD) guidance.⁵⁵ However, given the length of the review period, variations in the methodology such as differences in search strategies and eligibility criteria, are to be expected and must be acknowledged. A summary of the EAG's critique of the methods is provided in Table 4:1.

Table 4:1: Summary of the EAG'S critique of the methods implemented by the Company to conduct the economic systematic literature review

Systematic review stage	Section in the CS where methods are reported	EAG's assessment of the robustness of the methods
Data sources	CS Appendix E.1.1.1.3 ⁹²	Appropriate An appropriate range of bibliographic databases were used. Additionally, grey literature was searched together with an appropriate range of conference proceedings and clinical trials registries.

Systematic review stage	Section in the CS where methods are reported	EAG's assessment of the robustness of the methods
Search strategies	CS Appendix E.1.1.1.3 ⁹²	Some concerns The EAG concludes this a very narrow search, although this might have been a pragmatic decision given the number of included studies. See Section 4.1.1 for further information.
Search filters	CS Appendix E.1.1.1.3 ⁹²	Some concerns The EAG has identified that either a modified or outdated CADTH filter was used. See Section 4.1.1 for further information.
Inclusion criteria	CS, Section 3.1; ⁶ Appendix E.1.2.1; ⁹² CS Appendix F.1.2.1 ⁹⁴	Some Concerns The eligibility criteria for the population remained consistent throughout the original SLR and subsequent updates, while presenting a narrower population stated in the NICE scope. ³¹ Variations in eligibility of the interventions and comparators, and study designs, are noted across SLR updates in addition to post-hoc amendments. See Section 4.1.1 for further information.
Study selection	CS Section 3.1; ⁶ CS Appendix E.1.2.2; ⁹² CS Appendix F.1.2.2 ⁹⁴	Some Concerns The selection of studies in the HRQoL SLR was well reported and transparently described. While for economic evaluations and cost/HCRU components, the Company stated an audit of excluded studies was unavailable from the first SLR update, which the EAG observed to lead to some uncertainties and discrepancies in the flow of articles depicted in the PRISMA diagram. See Section 4.1.4 for further information.
Data extraction	CS Section 3.1; ⁶ CS Appendix E.1.3; ⁹² CS Appendix F.1.3; ⁹⁴ CS Appendix G ⁹³	Appropriate Data extraction was reported to take place by the Company into a data extraction sheet using appropriate methods, while these were not provided as part of the CS, summaries of included economic evaluation study characteristics, modelling approaches and outputs were clearly reported. Additionally, summaries of study characteristics

Systematic review stage	Section in the CS where methods are reported	EAG's assessment of the robustness of the methods
		and outcomes from HRQoL studies as well as studies reporting cost and HCRU were provided. The EAG therefore considers the data extraction carried out to be appropriate.
Quality appraisal	CS Section 3.1; ⁶ CS Appendix E.1.4; ⁹² CS Appendix F.1.4 ⁹⁴	Appropriate Included economic evaluations were quality assessed using the Drummond checklist. ⁹⁵ Studies reporting cost and resource outcomes but did not include full economic evaluations, were not assessed. Only studies reporting the HRQoL/utility data and aligned to the NICE reference case were included and assessed informally regarding respondent selection and recruitment, response rates to instrument used, loss to follow-up, missing data and study limitations. As the latter were the only studies included in the economic model, the EAG consider this appropriate.
Evidence review	CS Section 3.1; ⁶ CS Appendix E 1.5; ⁹² CS Appendix F 1.5; ⁹⁴ CS Appendix G ⁹³	Some concerns A lack of economic evidence on mepolizumab with standard of care or dupilumab for the patients with moderate, severe or very severe COPD treated with triple therapy or dual therapy with add on therapies was reported. There is some uncertainty as to whether improvements in methods outlined above would have strengthened the economic evidence base. See Section 4.1.4 for further information.
Abbreviations: COPD = chronic obstructive pulmonary disease; CS = company submission; EAG = External Assessment Group; HRQoL = health-related quality of life; HCRU = healthcare resource use; PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses; SLR = systematic literature review		

4.1.1 Search methods

4.1.1.1 Search strategies

The search strategy is generally comprehensive in its use of COPD terms, however overall, the search is very broad and the EAG has concluded that it lacks the precision of the search used in the clinical effectiveness SLR.⁵⁴ Key issues include the absence of the terms for triple therapy ICS/LABA/LAMA, maintenance therapies or the intervention mepolizumab. Furthermore, the inclusion of non-specific severity and staging terms such as “moderate”, “severe”, “exacerbation\$” and the decision to not anchor “stage II/III/IV” to COPD terms potentially introduces substantial irrelevant literature.

The search strategies used for the 2025 SLR update (CS, Appendix E.1.3.4) appears to have been reused from the 2016 *De novo* SLR (CS, Appendix E.1.3.1) verbatim. Under PRESS guidelines,⁶⁰ search strategies should be re-evaluated at each update to ensure alignment with current terminology and indexing changes. The Company has not stated that searches were peer reviewed prior to the update’s searches being conducted, therefore there is no evidence of review or adaptation. Reusing the unmodified 2016 strategy introduces risks to both sensitivity and precision (e.g., not anchoring COPD terms to the non-specific severity and staging terms). As such, this limits the methodological robustness of the update searches.

4.1.1.2 Search filters

Similarly to the searches in the clinical effectiveness SLR, the Company used modified and potentially outdated search filters. Although mentioned and referenced in the CS, the EAG has not been able to identify fully whether the Company used a validated and published filter. The Company stated that they developed their own cost-effectiveness filter using The Scottish Intercollegiate Guidelines Network (SIGN), however there is very little similarity between the original and the filter used and the Company have not provided adequate justification for the need to modify the existing filters that were cited. As the EAG cannot test the search strategy, it is unable to comment on the sensitivity on the strategy for the retrieval of relevant studies. Without comprehensive

testing, it is difficult for the EAG to quantify the effects mentioned may have on the results.

4.1.2 Eligibility criteria

The eligibility criteria defined in the PICOS framework concerning the population was generally consistent for the three SLR components pertaining to economic evaluations, HCRU and costs, and HRQoL, including the SLR updates.⁹² However, this specified inclusion of adults (≥ 18 years) with a diagnosis of moderate to very severe COPD for ≥ 1 year as defined by clinical guidelines such as GOLD and ATS/ERS or caregivers to patients with moderate or severe COPD. As discussed in Section 2.3.1 the EAG highlight this definition represents a narrower population than that indicated in the NICE scope.³¹ Furthermore, during the review process of the original SLR post-hoc criteria were applied to the population criterion, a practice which can introduce selection bias.

For the HRQoL, HCRU and cost components restrictions to the eligibility criteria were not applied to the interventions and comparators across all SLR iterations. Studies were permitted to have non-pharmacological intervention, pharmacological intervention or none. While for economic evaluations, ICS-based maintenance triple or dual therapy regimen with or without add-ons were specified.⁹² Therefore oral therapies or non-pharmacological interventions including the five fundamentals of care specified in the NICE guidelines for COPD (NG115)¹ were not considered. Furthermore, while the eligibility criteria applied to the recent update included cost-consequence analysis, cost-offset analysis, and budget impact analysis, these study designs were not listed in the specified criteria for the original SLR, and two subsequent updates.⁹²

For the economic evidence, the original SLR applied post-hoc restrictive criteria during full-text review to publications from non-Asian countries (studies from Asian countries were excluded [i.e., Korea, Japan, China, Hong Kong, etc.]), which was applied in the first SLR update. While the second SLR update did not initially carry this forward, during full-text screening the

following countries of interest were specified: United States, Canada, all countries in Europe, China, Taiwan, South Korea, Singapore, Australia, and New Zealand, which was subsequently retained in the latest SLR update. Meanwhile in the original SLR and first update for the HQRoL component, restrictions were applied to non-Asian countries, which were lifted in the subsequent two updates. Studies that were initially excluded at the title/abstract and full-text screening stages based on geography in the latter SLR, were reported to have been rescreened during the subsequent SLR update; however, this process did not result in the identification of any additional eligible studies.

Since the eligibility criteria for inclusion of studies were not restricted by geography in the 2024 SLR, studies initially excluded due to reasons such as country not of interest (i.e., Asian countries) in the original 2016 SLR and 2018 SLR update at title/abstract and full-text screening stages were rescreened, however, no eligible studies were identified during re-screening.

For all SLR components, only publications in English were considered. Collectively the limitations described above regarding the list of interventions, study designs and post-hoc adjustments raises some concerns as to whether this may have impacted the identification of relevant evidence, especially regarding economic evaluations. While post-hoc adjustments may have inadvertently caused discrepancies during screening for eligibility, the EAG does also acknowledge these criteria have been clearly reported and may have helped focus the evidence selected to be more generalisable to the UK and to a defined patient population. Overall, the EAG has some concerns surrounding some of the restrictions applied to the eligibility criteria that may reduce the identification of supportive evidence relevant to the decision problem.

4.1.3 Study selection

Economic evaluations, HCRU and cost studies

In the first SLR update the Company stated an auditable record of excluded studies was unavailable, making it unclear as to which stage exclusions occurred,⁹² an essential requirement for accurate PRISMA documentation. During the second SLR update in July 2024, 100 records from the original and 2018 SLR update were stated by the Company to be re-screened mitigating some of the methodological inconsistencies in applied eligibility criteria, but only to the studies that were rescreened. Subsequently 41 of these records were excluded as they were published prior to 2014, and 18 were excluded as they reported no outcomes of interest.⁹² The PRISMA diagram further indicates an additional 50 conference proceedings and two records from reference cross checking in the original and first SLR update to included records but does not clarify at what stage these were identified, screened or included. The EAG also note a minor discrepancy in the number of articles included versus rescreened in the original SLR and its update (99 versus 100), as reflected in both the text and PRISMA diagrams.

While the original SLR and first SLR update were not originally transparent in their documentation, the two most recent SLR updates demonstrated improved transparency, and complete reference lists of included/excluded studies with reason for exclusion being provided. Overall, the EAG has some concerns over the methods taken during study selection in the initial SLR conducted. However, the EAG acknowledges the Company's attempt to reconcile the earlier evidence retrieved and rescreen using updated eligibility, and considering the most recent, and thus probably relevant evidence was reported well, the EAG finds the methods undertaken appropriate.

4.1.4 Evidence review

Economic evaluations

Overall, 48 economic evaluations reporting cost-effectiveness analyses were included (original SLR and 2018 update: n = 5; 2025 SLR update: n = 7; 2024

SLR update: n = 36). The critical appraisal judged economic evaluations to be of moderate to high methodological quality, with well-defined questions, clear comparator descriptions, appropriately reported model parameters (including time horizons and discounting), and performed incremental analyses. Across included economic evaluations, 28 were from a European perspective (UK: n = 18), while 11 were from a US/Canada perspective, 8 from China and 1 from Singapore (Table 22, CS Appendix E⁹²). A range of treatments were assessed however, no economic evaluations were identified evaluating mepolizumab compared with standard of care or dupilumab for the patients with moderate, severe or very severe COPD treated with triple therapy (ICS/LABA+LAMA) or dual therapy with add on therapies.

HCRU and Cost studies

Overall, 25 studies out of all 198 included studies in the economic SLR reporting cost and HCRU outcomes, were indicated to report data from a UK setting and thus considered relevant to this technology appraisal.⁹² The remaining 173 studies were excluded from the UK-based HCRU and cost data presented in Appendix G of the CS.⁹³ Included study and baseline population characteristics were presented, stratified by studies reporting outcomes for acute exacerbation of COPD (AECOPD, n = 5) and moderate to severe COPD (n = 20) (Table 1, Appendix G⁹³).

HRQoL

In total 85 HRQoL studies assessing indirect and direct utility measures were identified for moderate to very severe COPD patients, and for carers of patients with COPD. The Company presented an assessment of all included HRQoL studies against the NICE reference case criteria (see Table 38 in CS Appendix F ⁹⁴), which was considered to be met if utility values were derived from a population generalisable to the UK population or from UK tariff (providing studies used a preference-based measure and an appropriate method for valuing health states). Overall, 22 studies were reported to align to the NICE reference case, out of which seven also reported utilities for exacerbation health states.

EAG comment: The EAG acknowledges the clear lack of economic evidence on mepolizumab with SoC or dupilumab for the patients with moderate, severe or very severe COPD treated with triple therapy (ICS/LABA+LAMA) or dual therapy with add-on therapies. However, considering some of the limitations highlighted above in Sections 4.1.1, 4.1.2 and 4.1.3, improvements in the search and screening strategy could have increased the sensitivity and precision of the reviews, which in turn could have yielded a more comprehensive evidence base that more broadly aligned with the NICE decision problem.

4.2 Critique of the submitted economic evaluation

4.2.1 NICE reference case checklist

The Company's economic evaluation for the base-case analysis was evaluated against the NICE reference case checklist⁵⁶ and the findings are summarised below in Table 4:2.

Table 4:2: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on Company's submission
Perspective on outcomes	All direct health effects to the individual receiving healthcare or, when relevant carers.	Appropriate Carer QALY not considered in the model because of lack of evidence.
Perspective on costs	NHS and PSS	Appropriate Indirect costs were not considered in the base-case analysis; however exploratory analysis incorporating the costs associated with productivity loss and early retirement was conducted. There are concerns regarding the correctness and appropriateness of the parameters used in this exploratory analysis.
Type of economic evaluation	Cost utility analysis.	Appropriate In addition, the Company also provided a cost

Element of health technology assessment	Reference case	EAG comment on Company's submission
		comparison analysis between mepolizumab and dupilumab.
Time horizon	Sufficiently long enough to capture all relevant differences in costs and health outcomes between the technologies being compared.	Appropriate 30 years (lifetime for the starting cohort of 65.4 years of age).
Synthesis of evidence on health effects	Based on systematic review methods and appropriate meta-analytic technique.	Appropriate Adheres to the reference case; IPD and MAIC methodology was used.
Measuring and valuing health effects	Express health effects in QALYs, and the preferred measure is the EQ-5D in adults, with mapping to EQ-5D when alternative measures used.	Appropriate Age adjusted utilities were applied using the values derived from Hernandez Alava et al. 2022 ⁹⁶ , with disutility values informed by pooled EQ-5D-3L data from MATINEE, METREX and METREO and IMPACT studies. Alternative EQ-5D weights derived from individual SGRQ scores from pooled mITT-300 population plus IMPACT and ECLIPSE studies were explored in the scenario analysis.
Source of data for measurement of health-related quality of life	Report the measurement of changes in health-related quality of life directly from patients and carers (if appropriate).	Appropriate As above, pooled EQ-5D data from the trials were used.
Source of preference data for valuation of changes in health-related quality of life	Valued using EQ-5D with UK general population preference weights.	Appropriate Age adjusted utilities derived using UK general population utilities; additional scenario analysis has been undertaken to account for uncertainties.
Equity considerations	All QALYs are valued equally, regardless of who gains them.	Appropriate Equity concerns were not explored in the model.
Evidence on resource use and costs	Resource use and cost data should have been generated and presented systematically and should reflect the NHS and PSS.	Appropriate Adheres to NICE reference case.

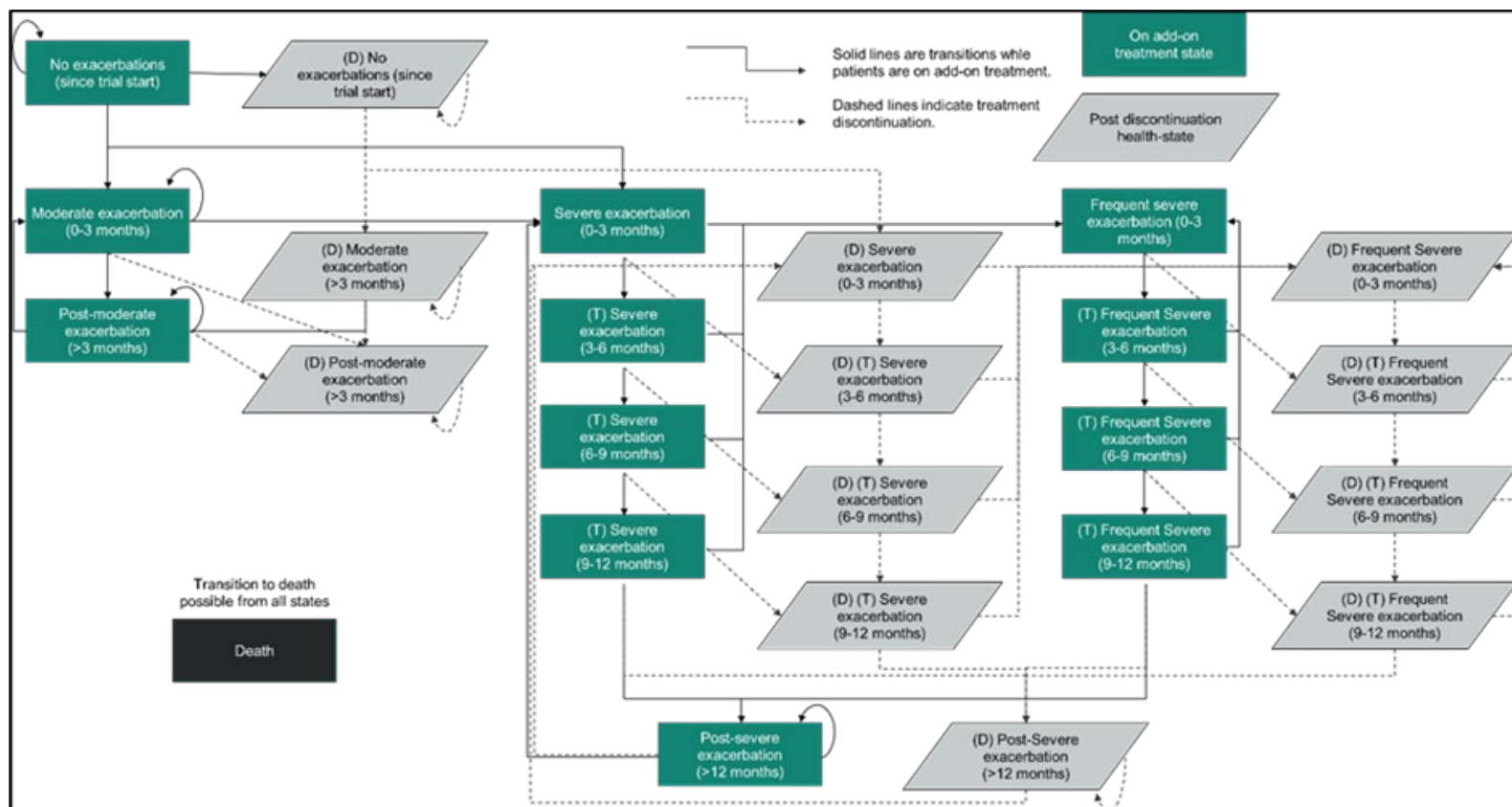
Element of health technology assessment	Reference case	EAG comment on Company's submission
Discounting	Annual discount rate of 3.5% for both the costs and outcomes.	Appropriate Annual discount rate of 3.5% was applied to costs and outcomes in the Company model.
Source: NICE methods guideline ⁵⁶ , CS ⁶ Abbreviations: EAG = External Assessment Group; PSS = Personal Social Services; QALY = Quality Adjusted Life Year.		

4.2.2 Model structure

4.2.2.1 Type of model

A *de-novo* cost-utility analysis (CUA) model was developed and programmed in Microsoft Excel using a Markov model structure (Figure 4.1). The Markov model uses a lifetime horizon (30 years) and 3-monthly model cycles to reflect the impact of COPD exacerbations on outcomes such as mortality, health care resource utilisation, HRQoL and future risk of exacerbations.

Figure 4.1: Model structure in the Company submission



Note: a proportion of patients in the severe exacerbation health state (and associated tunnel states) will experience a moderate exacerbation (additional resource use). (D) – indicates a post-discontinuation health state, (T) indicates a tunnel state which will empty at the end of each model cycle.
Source: CS, Figure 11⁶

4.2.2.2 Health state and transitions

The Markov model included 13 health states, along with 12 additional discontinuation health states that mirrored the original health states. The model's health states were defined according to the exacerbation status, distinguished by severity (moderate or severe) and by time since exacerbation.

All patients entered the model in the "no exacerbations" health state and remained in this state until they experienced their first exacerbation event (moderate or severe), or discontinue from treatment, or die.

Patients entering the moderate exacerbation (0-3 months) state, in the next cycle, continue to remain in the same state if they experienced another moderate exacerbation, transitioned to the post-moderate exacerbation (≥ 3 months) if they remained exacerbation free, moved to the severe exacerbation (0-3 months) state if they experienced a severe exacerbation, discontinue treatment or die. Patients in the post-moderate exacerbation (≥ 3 months) state continued to be at risk of another exacerbation in each model cycle.

Patients in the severe exacerbation (0-3 months) state who did not experience a further exacerbation transitioned through a series of tunnel states (severe exacerbation (3-6 months), severe exacerbation (6-9 months), and severe exacerbation (9-12 months)), reflecting time since their severe exacerbation. Patients experiencing another severe exacerbation moved to the frequent severe exacerbations (0-3 months) state, while others could discontinue the treatment or die. Patients who remained exacerbation free and alive for 12 months transitioned to the post-severe exacerbation (>12 months) state, where they continued to be at risk of another severe exacerbation in each model cycle and could return to severe exacerbation (0-3 months) state. Patients in severe exacerbation states were assumed not to return to the moderate exacerbation (0-3 months) state, as severe exacerbation was considered a more significant factor in predicting patient outcomes than a moderate exacerbation.

Patients entering the frequent severe exacerbation (0-3 months) state, in the next cycle transitioned through tunnel states (frequent severe exacerbation (3-6 months, 6-9 months, and 9-12 months) if they experience subsequent exacerbation, or could discontinue treatment or die. Patients remaining exacerbation free and alive for 12 months transitioned to the post-severe exacerbation (>12 months) state, where they remained at risk of another severe exacerbation in each model cycle, and could transition back to the severe (0-3 months state).

Patients who discontinued the treatment (discontinuation applied only to mepolizumab or dupilumab treatment, not for SoC) transitioned to the corresponding discontinuation health state, where they are assigned the same exacerbation risk and impact as patients receiving SoC treatment.

Death was modelled as an absorbing state; background mortality was applied to all other health states.

EAG Comment: The EAG considers the modelling approach appropriate and notes that sufficient detail is provided on patient transitions. However, some of the assumptions made by the Company regarding parameters may increase structural uncertainty. Comments on these parameters are provided in the sections below.

4.2.3 Population

The patient population included in the Company's base-case were adults with uncontrolled COPD of an eosinophilic phenotype (defined as BEC ≥ 300 cells/ μ L) who were receiving triple inhaled therapy (ICS, a LABA, and a LAMA). This population corresponds to the pooled mITT-300 population, which was informed by data from three phase 3 trials (MATINEE, METREO and METREX) using a pooled analysis of mepolizumab SC versus placebo SC treatments. It included all the participants from MATINEE, as well as participants from METREX and METREO who had a BEC ≥ 300 cells/ μ L at

screening, were on triple inhaled therapy (ICS, LAMA and LABA), met all inclusion criteria of their respective trials and received at least one dose of study treatment (see Section 3.2). These patients had a clinical diagnosis of COPD for at least 12 months prior to enrolment, with moderate to very severe disease (informed by GOLD stages 2 – 4), and had experienced either two or more moderate exacerbations (treated with systemic corticosteroids with or without antibiotics) or at least one severe exacerbation (requiring hospitalisation) in the previous 12 months.⁶

The baseline characteristics of the patients in the Company submitted economic model were informed by this pooled mITT-300 population data and, the IMPACT and ECLIPSE studies (Table 4:3). The majority of patients considered were male (69%) and presented with moderate or severe COPD.⁶ The mean age of the patient population was 65.4 years. The proportion of patients with moderate, severe and very severe patients are provided in Table 4:3. It was verified by the EAG that the discrepancy in the total severity proportions not adding up to 100 was due to rounding error in the Company submission.

Table 4:3: Baseline characteristics of patient population in the Company base-case.

Population characteristic	Value in Company base-case*
Mean age (years)	65.4
Sex (% female)	31.0
COPD Severity by FEV1% predicted*	
Moderate: ≥50%–≤80% predicted	46.7
Severe: ≥30%–<50% predicted	40.4
Very Severe: <30% predicted	12.8
Source: CS document, Section 3.3.1, Table 47 ⁶ Abbreviations: COPD = chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in 1 second. *Total does not add up to 100% exactly, because of rounding of the percentages.	

EAG Comment: The EAG consulted a clinical expert to validate the patient population considered in the Company’s base-case model. The expert noted that, in clinical practice, a patient does not need to present with a BSE threshold ≥300 cells/μL to be considered as having uncontrolled COPD; this is

instead defined by disease severity and the incidence of moderate or severe exacerbations. Nevertheless, the clinician considered the population and baseline characteristics included in the economic evaluation to be appropriate and representative of the UK COPD population.

The IMPACT and the ECLIPSE trials included the treatment with SoC but not the biologics. The EAG had raised this issue in the clarification call and the justification by the Company was that these two trials were included to increase the sample size for analysis. Section 3.1.5 discusses the inclusion of these trials in the pooled analysis.

Whilst the EAG acknowledges that COPD largely affects older adults, at the PfC¹² the EAG requested that the Company present a scenario analysis for a younger population group (aged 40-64 years). This request was made because this group had a higher risk ratio (0.93) for moderate/severe exacerbations compared with the older population modelled in the Company's base-case analysis (see CS, Section 2.8.1, Figure 10⁶). In their response (B10),¹² the Company provided a scenario analysis using the younger population and the corresponding parameters available for this group. This scenario analysis had a large impact on the ICER observed in the Company base-case analysis (see scenario 28, Table 4:28, Section 4.3.2.3).

4.2.4 Intervention and comparators

Intervention: Mepolizumab 100mg in combination with triple inhaled therapy (which is the SoC) is administered SC every 4 weeks up until 52 weeks, after which the responders continue on the same treatment.⁶

Comparators: The comparator in the cost-effectiveness analysis was SoC which included the triple inhaled therapy.⁶

Dupilumab, 300 mg SC every 2 weeks (Q2W), in combination with the SoC (triple therapy, or double therapy if the triple therapy was not appropriate) was

undergoing NICE appraisal as add-on treatment for uncontrolled COPD.²⁵ Therefore, the Company undertook a pragmatic approach to consider dupilumab as a relevant comparator. The MAIC conducted by the Company indicated that there were no statistically significant differences between mepolizumab and dupilumab for the outcomes analysed.⁶ Consequently, the Company also submitted a cost comparison analysis of mepolizumab + SoC versus dupilumab + SoC.

The CS included comparators listed in the NICE scope³¹ except roflumilast and azithromycin. The justification for excluding roflumilast was that it is rarely used in UK clinical practice due to poor tolerability and safety concerns.⁶ Long-term azithromycin use is limited to infection-driven COPD in the UK and is constrained by safety and monitoring requirements. Therefore, it was also excluded as a relevant comparator.⁶

EAG Comment: In current UK clinical practice, there are no routinely available long-term add-on maintenance therapies for uncontrolled COPD.³¹ Therefore, the clinical expert could not validate the intervention regimen in this submission. However, the clinical expert consulted by the EAG was of the opinion that, given the mechanism of action and the positioning of mepolizumab, the treatment regimen appeared reasonable. In the MATINEE trial, the stopping rule specified that only responders at week 52 continued on treatment.⁶ Accordingly, in the Company's base-case, responders were assumed to receive mepolizumab for the full time-horizon;⁹⁷ the EAG considered this to be an appropriate assumption, given the available evidence.

Triple inhaled therapy with ICS, LABA and LAMA is the standard long-term treatment for COPD patients in the UK.³¹ Therefore, the EAG considers this as a relevant comparator for mepolizumab treatment. Patients were assumed to receive triple inhaled therapy for their lifetime in the Company model, and this assumption was validated by the clinical expert consulted by the EAG. Considering dupilumab as a comparator in the submission was an appropriate

approach by the Company. The NICE scope listed roflumilast and azithromycin, with the caveat that they are used only in specific subgroups of COPD patients and are associated with safety concerns regarding long-term use.³¹ According to the clinical expert consulted by the EAG, these treatments are not commonly used in UK clinical setting. Therefore, the EAG considered the exclusion of roflumilast and azithromycin to be a reasonable approach.

4.2.5 Treatment effectiveness and extrapolation

The clinical inputs included in the economic model comprised baseline characteristics, exacerbation rates, responder rates and discontinuation rates for both mepolizumab and dupilumab.

As reported in Section 4.2.3, the economic model used the patient baseline characteristics consistent with those from the pooled trial analysis, which included mITT-300 population from the mepolizumab studies (MATINEE, METREX, METREO), as well as the IMPACT and ECLIPSE studies.⁹⁷ The mean age of 65.4 years was reported to be aligned with the mean age of COPD patients across Europe (66 years) and with the mean age observed in the pooled BOREAS and NOTUS studies (65.1 years).

4.2.5.1 Responder rates

A stopping rule was implemented in the economic model at 52-weeks, whereby only patients who responded to the treatment remained on treatment beyond 52 weeks. As in the dupilumab submission,¹⁸ response to treatment was defined as having fewer or equal number of severe or moderate exacerbations compared with the previous year.

Responder rates for mepolizumab were based on the response rates observed in pooled mITT-300 (Table 4:4). As there was no evidence for dupilumab by exacerbation criteria, the overall 52-week response rate for

Non-responders were assumed to discontinue the treatment after 52 weeks and to receive background therapy, with the corresponding costs and clinical outcomes applied in the economic model.

Health state	No. of evaluable patients in each health state (out of mepolizumab population from pooled mITT-300)*	No. of patients meeting response criteria - mepolizumab (%)	Proportion meeting response criteria – dupilumab (%)
No exacerbations (baseline)	■	■	■
One or more moderate exacerbations (no severe)	■	■	■
Any moderate and 1 severe exacerbation †	■	■	■
Any moderate and 2 or more severe exacerbations‡	■	■	■

† This informs the ‘severe exacerbation’ and ‘post severe exacerbation’ states in the model ‡This informs the ‘frequent severe exacerbation’ states in the model. *Meaning those on treatment at 52 weeks.

Abbreviations: CEM = Cost-effectiveness model; ITT = intention-to-treat; mITT = modified-intention-to-treat.

Source: CS, Table 48⁶

160

versus dupilumab) across all the health states may bias the estimated response rates for dupilumab, particularly when health states differ in terms of exacerbation severity.

4.2.5.2 Exacerbation rates:

The rates of moderate and severe exacerbations were used to capture the disease progression in the economic model. The first exacerbation (moderate or severe), as well as the subsequent exacerbations for the background therapy, were informed by the pooled analysis of COPD trials including MATINEE, METREX, METREO, ECLIPSE and IMPACT) aligning with the population characteristics used in the economic model (Table 4:5). Scenario analyses were performed using higher first exacerbation rates derived from the reported rates 12 months prior to randomisation in the MATINEE trial and from post-randomisation rates in the METREX and METREO trials.

Table 4:5: Background therapy first exacerbation rates used in the Company’s model (base-case and scenario analysis)

Exacerbation type	Rate of first moderate exacerbation (95% CI)	Rate of first severe exacerbation (95% CI)
Base-case		
Pooled trial analysis post-randomization period	0.92 (0.85, 0.99)	0.17 (0.14, 0.20)
Scenario analysis		
Scenario 1: Calibrated rate to achieve first-year model prediction equal to the rate in the year prior to randomization in MATINEE	1.58 (1.51, 1.66)	0.29 (0.25, 0.34)
Scenario 2: METREX/METREO post-randomization period	1.43 (1.19, 1.68)	0.20 (0.10, 0.29)
Source: CS, Table 49 and Table 50 ⁶ Abbreviations: CI, confidence interval		

The Company applied rate ratios (estimated relative to the “no exacerbation” health state and derived from the pooled analysis of COPD trials (MATINEE, METREX, METREO, ECLIPSE and IMPACT) to the background therapy first

moderate and severe exacerbation rates to derive subsequent moderate and severe exacerbation rates (Table 4:6).

The Company converted all annual exacerbation estimates to quarterly rates and applied these in each model cycle after transforming them into 3-month probabilities.

Table 4:6: Rate Ratios for subsequent exacerbations in the Company's economic model

Health State	RR of subsequent moderate exacerbation (95% CI)	RR of subsequent severe exacerbation (95% CI)
No exacerbations	Reference	Reference
Moderate exacerbations (0–3 months)		
Moderate exacerbations (>3 months)		
Severe exacerbations (0–3 months)		
Severe exacerbations (3–6 months)		
Severe exacerbations (6–9 months)		
Severe exacerbations (9–12 months)		
Frequent severe exacerbations (0–3 months)		
Frequent severe exacerbations (3–6 months)		
Frequent severe exacerbations (6–9 months)		
Frequent severe exacerbations (9–12 months)		
Post severe exacerbations (>12 months)		
Source: CS, Table 51 ⁶ Abbreviations: CI = confidence interval; RR = rate ratio.		

EAG Comment: The EAG considers the approach to using rate ratios to adjust baseline moderate and severe exacerbation rates in subsequent exacerbation health states to be appropriate and consistent with standard modelling practice, and a recognised method for capturing the increased risks

in exacerbations following an exacerbation. The conversion of annual exacerbation rates into probabilities for use in 3-monthly model cycles was methodologically appropriate.

4.2.5.3 Exacerbation rate treatment effect (Year 1)

The Company derived the Year 1 rate ratios for moderate and severe exacerbations for mepolizumab from pooled mITT-300 trials and applied them to the background therapy exacerbation rates to generate the model's cycle specific transition probabilities (Table 4:7). Scenario analyses with alternative risk ratios for mepolizumab were also considered; the first scenario used MATINEE trial data in isolation, and the second scenario considered first and subsequent exacerbations separately, assuming the treatment effect on subsequent exacerbations were equal to that on first exacerbations.

Table 4:7: Treatment effect for exacerbation rates, mepolizumab vs background therapy (base-case and scenario analyses) used in Company's economic model

Exacerbation type	Rate for moderate exacerbation (95% CI)	Rate for severe exacerbation (95% CI)
Base-case		
Pooled mITT-300 population		
Scenarios		
Scenario 1: MATINEE only	0.79 (0.65, 0.96)	0.66 (0.43, 1.01)
Scenario 2: pooled mITT-300, subsequent exacerbations assumed equal to first exacerbations and used separately		
Abbreviations: CI = confidence interval; mITT-300 = modified intention-to-treat 300 (participants with BEC $\geq$ 300 cells/ μ L at screening who received $\geq$ 1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline. Source: CS, Table 52 and Table 53. ⁶		

The Company applied MAIC informed risk ratios to the mepolizumab exacerbation rates for moderate and severe exacerbations to derive the corresponding rates for dupilumab (Table 4:8). The risk of a severe

exacerbation for dupilumab+SoC was calculated by directly applying the between treatment rate ratio for severe exacerbations to the mepolizumab severe exacerbation rate. As the MAIC estimated rate ratios only for moderate/severe exacerbations and for severe exacerbations, the moderate exacerbation rate for dupilumab in each model cycle were derived as: the total exacerbation risk for dupilumab (estimated by applying the MAIC generated rate ratio for total exacerbation to the corresponding mepolizumab total exacerbation rate, calculated as the sum of the moderate and severe rates) minus the directly estimated dupilumab severe exacerbation rate.

Table 4:8: Treatment effect for exacerbation rates, mepolizumab vs dupilumab used in the Company’s economic model.

Exacerbation type	RR for moderate/severe exacerbation (95% CI)	RR for severe exacerbation (95% CI)
Mepolizumab vs. dupilumab	0.91 (0.60, 1.37)	0.68 (0.27, 1.72)
Abbreviations: CI = confidence interval; RR = rate ratio. Source: CS, Table 54 ⁶		

In their base-case analysis, the Company used MAIC analysis where CB was based on investigator responses. The rationale provided for this decision was that in the BOREAS and NOTUS trials, which inform the MAIC, CB was defined through investigator assessment of patient symptoms rather than patient self-report via the SGRQ and this aligned more closely with the investigator assessed definition used in the MATINEE trial. In addition, in the mepolizumab trials, after restricting the population based on the BOREAS/ NOTUS inclusion criteria used in the MAIC, higher mean baseline SGRQ scores were observed compared with BOREAS/ NOTUS trials, regardless of the CB definitions. However, this difference was smaller when CB was defined using the investigator assessment than the SGRQ. A scenario analysis was conducted using the MAIC in which CB was defined based on SGRQ responses.

EAG comment: The EAG considers the Company's approach to applying treatment effects for exacerbation rates in both the base-case and the scenario analyses to be methodologically appropriate. The Company also acknowledges that assuming the same risk ratios for subsequent exacerbations as for first exacerbations and modelling them separately in the scenario analysis may be optimistic, as the larger reduction observed for first exacerbations compared with the base-case (where first and subsequent events are pooled) may overestimate the treatment benefit.

At the PfC,¹² the EAG suggested that the ML-NMR would be more suitable than the MAIC for estimating risk ratios for exacerbations. In its response (A2),⁹⁸ the Company updated the analysis using ML-NMR derived risk ratios, and conducted a scenario analysis to assess these in the economic model. This update, however, had no material impact on both the deterministic and probabilistic ICERs observed in the Company's base-case (see Section 4.3.2.3, Scenario 30, Table 4:28).

4.2.5.4 Exacerbation rate treatment effect (responders)

For mepolizumab, from Year 2 onwards, the Company's base-case model applied the rate ratios of moderate and severe exacerbations for responders versus baseline, estimated at 52 weeks from the pooled mITT-300 population (

Table 4:9). A scenario analysis was also conducted using the responder rate ratios from the MATINEE trial only (

Table 4:9). However, in both the base-case and scenario analysis, the treatment effect for responders was assumed to be the same across the moderate exacerbation states (0-3 months and ≥ 3 months) and the severe exacerbations states (all severe/frequent severe states) due to insufficient observations to estimate effects for each health state.

Table 4:9: Rate Ratios for exacerbations in responders used in the Company's economic model

Health state	RR of moderate exacerbation; responders (95% CI)	RR of severe exacerbation; responders (95% CI)
Base-case (pooled mITT-300 population)		
Mepolizumab		
Scenario (MATINEE only)		
Mepolizumab		
Abbreviations: CI= confidence interval; mITT-300 = modified intention-to-treat 300 (participants with BEC $\geq$ 300 cells/ μ L at screening who received $\geq$ 1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline; RR = rate ratio. Source: CS, Table 55 and Table 56. ⁶		

For dupilumab, from Year 2 onwards, the Company's approach aligned with that outlined above for the treatment effect for dupilumab in Year 1, where rate ratios from the MAIC were applied to the mepolizumab responder exacerbation rates and adjusted to estimate three-monthly probabilities for moderate and severe exacerbations. The Company adopted this approach because the responder rate ratios from the dupilumab submission were redacted. However, the Company acknowledges the uncertainty in their approach, as the MAIC risk ratios were aligned with the dupilumab trial data but were applied to responder rates from the mepolizumab trial population, which represents a different and broader population.

EAG Comment: The EAG considers the Company's approach to modelling the treatment effect for mepolizumab from Year 2 onwards, applying rate ratios of moderate and severe exacerbations for responders derived from pooled mITT-300 population at 52 weeks and with a scenario analysis using rate ratios from the MATINEE trial, to be appropriate. Due to insufficient observations to generate separate estimates for each state, the Company assumed identical treatment effects across all moderate and severe exacerbation states. Whilst the EAG acknowledges the challenges associated with insufficient data, given the clinical differentiation between moderate and severe exacerbations and the potential for treatment effects to vary across

these states, the assumption of equal treatment effects may introduce structural uncertainty in the economic model.

The EAG considers that applying rate ratios from the MAIC, which were aligned with the dupilumab trial population, to responder rates from the mepolizumab trial population may introduce a high risk of bias and raise concerns about the face validity of the approach. Nevertheless, the EAG acknowledges that this may be a pragmatic solution in the absence of suitable data.

4.2.6 Treatment discontinuation

The treatment discontinuations for mepolizumab in the first year of the Company's base-case economic model were sourced from pooled mITT-300 trial data (Table 4:10). For dupilumab, the Company assumed a 9.3% discontinuation probability in the first year, informed by the dupilumab committee papers¹⁸ based on 52-week discontinuation rate observed in the pooled BOREAS and NOTUS trials; and converted it to a 2.41% probability of discontinuation in each three-month cycle in the model.

Table 4:10: Probability of treatment discontinuation for mepolizumab in Year1 of Company's base-case economic model.

Time period	Total number of patients on mepolizumab	Number of patients who discontinue mepolizumab	Probability of mepolizumab discontinuation
0–3 months	■	■	■
4–6 months	■	■	■
7–9 months	■	■	■
10–12 months	■	■	■
Source: CS, Table 57 ⁶			

Among the three trials in mITT-300, only the MATINEE trial had a follow-up beyond 12 months, therefore the Company used the annual discontinuation rate for responders in the second year of MATINEE trial (adjusted for patient years of follow-up) to derive the per cycle probability of discontinuation for

mepolizumab in the base-case (Table 4:11). The Company assumed the same discontinuation probability for dupilumab. In addition, the Company explored alternative discontinuation rates in scenario analysis for Year 2 onwards. A 15% annual discontinuation rate (equating to 3.68% probability per model cycle), sourced from the dupilumab NICE Company submission¹⁸ and based on real-world evidence from an asthma study and clinical expert opinion, and ■■■% probability discontinuation per cycle from MATINEE were both applied to mepolizumab and dupilumab in these scenario analyses. The real-world evidence reported in the dupilumab NICE Company submission¹⁸ indicated discontinuation rates ranging between 15% and 25.8%, however, the Company only explored the lower bound (15%) in their scenario analysis.

The Company also assumed the same discontinuation probabilities across health states and these probabilities were assumed to remain constant for the full-time horizon from year 2 onwards.

Table 4:11: Probability of treatment discontinuation mepolizumab in Year 2 of the Company’s base-case economic model

	Probability of mepolizumab discontinuation (SE)
Annual discontinuation rate from MATINEE trial	■■■■■
Probability of discontinuation per cycle	■■■
Abbreviations: SE = standard error. Source: CS, Table 58 ⁶	

EAG comment: The EAG considers the Company’s approach to deriving Year 1 discontinuation rates for mepolizumab from the pooled mITT-300 trial data and for dupilumab from committee papers drawing on the pooled BOREAS and NOTUS trials to be appropriate. However, any differences in trial design and patient characteristics between BOREAS/NOTUS and mITT300 trials, may have introduced uncertainty within the economic model. At the PfC,¹² the EAG requested the Company provide a scenario analysis excluding COVID-19 related discontinuations from the discontinuation probability used for dupilumab (9.3%). In its response (B3),¹² the Company

argued that the 9.3% discontinuation rate, which includes COVID-19 related discontinuations, better reflects real-world practice, given the ongoing presence of COVID infection, which the EAG acknowledges. Nevertheless, the Company provided a scenario analysis using a reduced discontinuation probability (8.5%) after excluding COVID-related discontinuations. The scenario had no material impact on the Company's base-case results (see Section 4.3.2.3, Scenario 24, Table 4:26 Table 4:29 and Table 4:30).

The EAG considers the Company's approach to using MATINEE trial data to inform Year 2 discontinuation rates for mepolizumab to be reasonable, given that it is the only trial in the mITT-300 population with follow-up beyond 12 months. However, the assumption that dupilumab also has the same discontinuation probability as mepolizumab may not reflect potential differences in patient characteristics between these treatments. The scenario analyses exploring alternative discontinuation rates for Year 2 onwards are appropriate to address uncertainty. Nevertheless, by not exploring the higher bound of real-world discontinuation rates (25.8%), the Company may have underestimated the potential impact of higher discontinuation. The EAG has conducted an additional scenario analysis using the higher bound discontinuation rates (25.8%) (see Section 4.4.2, Scenario 3,

Table 4:32 and Table 4:33). Additionally at the PfC,¹² given the uncertainty in discontinuation rate beyond 2 years, the EAG requested that the Company provide a scenario analysis exploring the impact of applying 10-12 months discontinuation rate for 2 years and beyond, which may better represent the pooled mITT trial population. In its response (B4),¹² the Company stated that the data beyond 1 year from MATINEE (representing discontinuation among responders) was more appropriate, as this aligned with the incorporation of a stopping rule in the model, whereby only responders remained on mepolizumab from year 2 onwards. The EAG accepts the Company's argument. Nevertheless, the Company provided a scenario analysis applying a [REDACTED] discontinuation probability per cycle beyond 1 year, to both mepolizumab and dupilumab. This scenario had no material impact on the Company's base-case results. (see Section 4.3.2.3, Scenario 25, Table 4:29 and Table 4:30) However, the assumption of equal discontinuation probabilities across all health states and the assumption these probabilities remain constant from Year 2 onwards may introduce structural uncertainty, as discontinuation rate may vary by disease severity or over time. Nevertheless, the EAG acknowledges the limited availability of the evidence to inform these parameters.

In addition, at the PfC,¹² the EAG requested clarification from the Company on whether it had considered extrapolating the trial data using parametric fitting on the proportion of patients discontinuing mepolizumab and asked the Company to provide corresponding parametric fits. In its response (question B5),¹² the Company provided the Kaplan-Meier observed data for time to discontinuation with mepolizumab from week 52, along with extrapolated survival curves based on fitted parametric models. The Company argued that, although all the parametric models showed similar fit within the observed part of the data, there was substantial variation in the discontinuation predicted over the longer term across the distributions, highlighting considerable uncertainty in extrapolating the discontinuation beyond 52 weeks. Consequently, extrapolation of discontinuation data beyond 52 weeks was not considered appropriate. In addition, the Company stated that discontinuation

was not a key driver of the model, as scenario analyses using alternative discontinuation rates had little impact on the Company's base-case analysis. The EAG agrees with the Company's argument.

4.2.7 Mortality

The Company considered three components to calculate the probabilities of death in each health state of the model: background mortality for patients after excluding the impact of COPD, a standardised mortality ratio reflecting the increased probability of death for COPD patients after excluding the impact of severe exacerbations, and a case-fatality rate for severe exacerbations.

4.2.7.1 Background mortality

Background mortality was sourced from the national life tables for England and Wales (2018-2020).¹⁷ The Company did not use more recent life tables to avoid capturing excess deaths in the general population due to the COVID-19 pandemic. To prevent double counting of COPD mortality, the Company adjusted the general population mortality data in the model by removing deaths associated with COPD, identified using ICD-10 codes J40-44.

4.2.7.2 COPD-related mortality

Consistent with the approach taken in previous NICE submissions,^{18,32} the Company applied a standardised mortality ratio (SMR) value of 2.50 (sourced from Samyshkin et al, 2014⁹⁹ for the severe COPD state). This SMR excluded mortality risk associated with hospital-treated exacerbations and was applied to the background mortality to calculate the probability for patients with severe COPD. The Company explored the impact of SMR by running a scenario analysis in which the SMR for COPD-mortality was not applied in the economic model.

4.2.7.3 Case fatality rate for severe exacerbations

The Company accounted for the increased risk of mortality associated with severe exacerbations by applying case fatality rates into the economic model; which is consistent with the approach preferred approach by the committee in the dupilumab NICE submission.¹⁸ A case fatality ratio (CFR) of 15.6%, sourced from Hoogendoorn et al. 2011,¹⁰⁰ was applied only in the severe and frequent exacerbation (0-3 months) health states in the Company's base-case model, reflecting the critical period during which mortality risk is highest following severe exacerbation. Hoogendoorn et al. 2011,¹⁰⁰ is a meta-analysis estimating mortality risks from severe exacerbations across six studies, and the Company also applied an age adjustment using a relative risk per additional year of age derived from the same source. After 3 months, mortality risk was assumed to return to background mortality. The Company explored the impact of uncertainty in the CFR by using a slightly slower (14.2%)¹⁰¹ value in the scenario analyses and the uncertainty around this parameter was also explored in one-way sensitivity analysis.

EAG comment: The EAG considers the Company's approach to sourcing background mortality from the 2018-2020 life tables for England and Wales and adjusting it by removing deaths attributable to COPD (to avoid double counting of COPD deaths) is reasonable and methodologically appropriate. However, a scenario analysis using a more recent life table to explore the potential impact of excess mortality from COVID in recent years would help quantify the impact of these assumptions on the cost-effectiveness outcomes. The EAG conducted a scenario analysis of the Company's base-case using the most recent available ONS life tables, which had no material impact on the Company's base-case analysis (see Section 4.4.2, Scenario 1,

Table 4:32 and Table 4:33).

The Company's application of an SMR of 2.50, along with a scenario analysis in which the SMR is not applied, is methodologically appropriate. The scenario analysis helps assess the sensitivity of the cost-effectiveness results to this assumption of SMR. However, the EAG notes that the SMR is sourced from a single study and is a source of parameter uncertainty. In the PfC,¹² the EAG requested justification for the use of a SMR value of 2.50 for severe COPD rather than 3.85 for very severe COPD, as reported by Samyshkin et al. 2014⁹⁹ and asked for a scenario analysis using the higher value of 3.85. In its response (question B1),¹² the Company stated that the SMR value of 2.5 was consistent with the source used in the roflumilast NICE submission and was similar to the SMR reported for patients with severe COPD (2.33) in Whittaker et al. 2024,¹⁰² which was used in dupilumab submission.¹⁸ The Company acknowledged that using a SMR value derived from severe COPD may be conservative, given that 46.7% of pooled mITT-300 trial population was classified as having moderate COPD, and applying a SMR of 3.85 would likely overestimate mortality because only 12.8% of the pooled mITT trial population had very severe COPD. Nevertheless, the Company conducted a scenario analysis using a SMR value of 3.85, which had only a minimal impact on the ICER (see Section 4.3.2.3, Scenario 22, Table 4:29 and Table 4:30). Therefore, the EAG accepts the Company's justification, and the scenario analyses provided and agrees that the ICER was robust to the use of a higher SMR value of 3.85. Furthermore, the use of a SMR value lower than 2.5 is unlikely to substantially affect the ICER observed in the Company's base-case analysis.

The EAG considers the Company's application of CFR to account for the increased mortality risk following severe exacerbations to be methodologically appropriate and consistent with previous NICE committee preferences for dupilumab. Applying CFR only within 0-3 month severe and frequent exacerbation health states reasonably reflects the acute period during which mortality risk is elevated following severe exacerbations. The Company also

used a 1.041 relative risk for each unit increase in age. However, the EAG notes that the CFR of 15.6% and age adjustments sourced from Hoogdendoorn et al. 2011¹⁰⁰ is based on studies with a most recent data from 2005, and none of the six studies included in the meta-analysis were conducted in the UK population. The Company conducted a scenario analysis using a slightly lower CFR (14.2%) using the latest available UK data, however, the EAG considers that this only provides limited exploration of uncertainty. Therefore, at the PfC,¹² the EAG requested the Company provide a scenario analysis using a CFR of 14.2%, based on the NRAP 2021-23 data,¹⁰¹ with age adjustments informed by UK data reported in Samyshkin et al. 2014.⁹⁹ In its response (B2.c),¹² the Company conducted a scenario analysis. However, the ICER observed in the Company's base-case analysis were robust to this scenario analysis (see Section 4.3.2.3, Scenario 23, Table 4:29 and Table 4:30).

4.2.8 Health-related quality of life

EQ-5D-5L data collected in the METREX, METREO, and IMPACT studies were cross-walked to EQ-5D-3L using the approach of Hernández et al. (2017),¹⁰³ as recommended in the NICE guidelines (2022).⁵⁶ These mapped data were then pooled with the EQ-5D-3L data from the MATINEE trial to estimate health state utility values. The resulting utilities were used to inform baseline utility values and health state associated disutilities in the cost-effectiveness analysis (Table 4:12).⁶ The utility decrements associated with moderate, severe and frequently severe health states were ■■■■■, ■■■■■ and ■■■■■, respectively, indicating that greater severity corresponds to a higher disutility. In the Company's model, these values were scaled to the 3-month cycle and adjusted for age to reflect the decline in HRQoL in the general population, while ensuring that health state utilities did not exceed population norms at a given age.⁹⁷ Finally, EQ-5D-3L values from Hernández et al., 2022¹⁰³ were used to inform age associated utility decrements in the cost-effectiveness analysis.⁶

Table 4:12: Utility values used in the Company base-case

Health State	Utility/disutility value: mean (SE)	95% CI (UB – LB)
No exacerbations	████	████████
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)	████	████████
Source: CS Section 3.4.5, Table 62 ⁶ Abbreviations: CI = confidence interval; LB = lower bound; SE = standard error; UB = upper bound		

EAG Comment: The EAG considers the Company’s approach for deriving health state utility values to be methodologically appropriate and aligned with NICE guidance.⁵⁶ For the tunnel states, the disutility values increase from 0-3 months to 3-6 months for the severe and frequent severe health states. Thereafter, the value decreased from 3-6 months to 6-9 months and finally to 9-12 months. At the PfC,¹² the EAG asked the Company to clarify why the disutility value █████ used for the “Frequent severe (9-12 months)” health state was lower than that for the “Frequent severe” health state in earlier months. In its response (B11),¹² the Company confirmed that the disutility value used was correct, however it noted the uncertainty associated with this estimate was because it was informed by **only** █████. Consequently, the Company conducted a scenario analysis in which the disutility in the “Frequent severe (9-12 months)” health state was assumed to be equal to that of the “Frequent severe (6-9 months)” health state. This scenario had no material impact on the Company’s base-case result (see Section 4.3.2.3, Scenario 29, Table 4:29 and Table 4:30).

4.2.8.1 Scenarios:

The Company conducted several scenarios on the calculation of HRQoL (Table 4:13) which included:

- A scenario without age-adjustment in the model.
- Alternative sources of utility values:
 - Jackson et al. 2024¹⁰⁴ where the data from ETHOS study were used to estimate the disutility values associated with exacerbations in moderate to severe COPD patients.
 - NICE TA461³² base-case utility values, which were the preferred estimates for EAG and Committee, informed by Hoogendoorn et al. 2011.¹⁰⁰ In this study, it was assumed that 4.5 months post exacerbation, utility values return to baseline. In the CS, this translates to the utility value returning to normal after one model cycle (3 months).
 - Individual SGRQ values from pooled analysis of mITT-300 population (MATINEE, METREX, METREO), IMPACT and ECLIPSE studies, were converted to EQ-5D weights using the method proposed by Starkie et al. 2011.^{6,105}

Table 4:13: Disutility values used for scenario analysis in the Company's economic model.

Health state	Mean disutilities		
	Scenario 1 Jackson et al., 2024 ¹⁰⁴	Scenario 2 Hoogendoorn et al., 2011 ¹⁰⁰	Scenario 3 SGRQ converted to EQ-5D ⁶
Moderate (0–3 months)	–0.055	–0.0166	
Post-moderate	–0.014	0	
Severe (0–3 months)	–0.090	–0.0482	
Severe (3–6 months)	–0.024	0	
Severe (6–9 months)	–0.024	0	

Health state	Mean disutilities		
	Scenario 1 Jackson et al., 2024 ¹⁰⁴	Scenario 2 Hoogendoorn et al., 2011 ¹⁰⁰	Scenario 3 SGRQ converted to EQ-5D ⁶
Severe (9–12 months)	–0.024	0	████
Post-severe (>12 months)	–0.024	0	████
Frequent severe (0–3 months)	–0.090	–0.0482	████
Frequent severe (3–6 months)	–0.024	0	████
Frequent severe (6–9 months)	–0.024	0	████
Frequent severe (9–12 months)	–0.024	0	████
Source: CS document, Section 3.4.5, Table 63 ⁶ Abbreviations: SGRQ, = St George's Respiratory Questionnaire.			

EAG Comment: A scenario using the utility values of NICE TA461³² was included to assess the impact on cost-effectiveness when the EAG and Committee preferred values from the relevant submission were applied. The EAG notes that the study by Hoogendoorn et al. (2011),¹⁰⁰ which is the source of utility values, did not use UK tariffs. Nevertheless, it was considered appropriate to include this scenario, as these values were also explored in prior NICE technology appraisals.^{18,32}

4.2.9 Resources and costs

The Company conducted a SLR to inform the health care resource utilisations and costs in their economic model; the SLR is already summarised and critiqued in Section 4.1. The Company's economic model included treatment acquisition costs, treatment administration costs, health state costs including the COPD management costs, exacerbation event costs, and miscellaneous costs (productivity loss, early retirement costs); the details on these costs are provided below. The costs were expressed in 2023/24 price year in GBP and were inflated to 2023/24 using the Personal Social Services Research Unit (PSSRU) inflation indices¹⁰⁶ when necessary.

4.2.9.1 Intervention and comparators' costs and resource use:

Treatment acquisition costs

The list price for mepolizumab is £840 per 100mg per 1 ml. In the economic model, the Company applied a confidential PAS discounted (at [REDACTED]) price for mepolizumab, at £[REDACTED] per 100 mg per 1ml solution. Dupilumab also has a confidential PAS discounted price, therefore, the Company used the list price of £1,264.89 per 300 mg. The background therapy, applied in both arms of the model, consisted of a basket of inhaler treatments, and was costed using the weighted average of their market shares, as outlined in the CS⁶ (see Table 4:14). The treatment costs per cycle were calculated based on the number of administrations required per cycle, in accordance with the SmPC for each treatment (

Table 4:14).

Table 4:14: Acquisition costs for intervention and comparator treatments used in the Company's economic model

Intervention	Pack size (mg)	Number of units	Price per pack	Dose per admin (mg)	Cost per model cycle
Mepolizumab	100	1	List price: £840.00 PAS price: £[REDACTED]	100 mg administered as a SC injection Q4W	£2,739.38 (List price) £[REDACTED] (PAS price)
Dupilumab	300	2	List price: £1,264.89	300mg administered as a SC injection Q2W	£4,125.01
Trelegy Ellipta(38.0% of background therapy)	Inhaler	30	£44.50	1 inhalation, QD	£135.45
Trimbow (59.4% of background therapy)		120	£44.50	2 inhalations, BID	
Trixeo aerosphere (2.6% of background therapy)		120	£44.50	2 inhalations BID	
Abbreviations: Abbreviations: BID = twice daily; PAS, patient access scheme; Q2W = every 2 weeks; Q4W = every 4 weeks; QD = once daily; SC = subcutaneous. Source: CS, Table 64. ⁶					

Treatment administration costs

The Company's base-case assumed that 95% of patients would self-administer mepolizumab and dupilumab (in line with the expert feedback provided to the EAG in the dupilumab NICE submission¹⁸), following a one-off training session delivered by a Band 5 hospital-based nurse. The remaining 5% of the patients were assumed to require administration support via a home nurse visit. The Company assumed that both the one-off training session and the home visit would require one hour of nurse time, costed at £52 based on the PSSRU¹⁰⁶ cost for a Band 5 hospital nurse. All patients (100%) were assumed to self-administer the background therapy consisting of inhalers.

EAG comment: The EAG considers the Company's estimation of treatment acquisition and administration costs appropriate. The Company's assumption of 5% of the patients requiring administration support via a home nurse visit was validated by the clinical expert the EAG contacted.

4.2.9.2 Health state costs

The Company's economic model health state costs consisted of routine COPD management costs, exacerbation management costs, and other miscellaneous costs (productivity loss and early retirement costs). The Company acknowledged the elevated risk of cardiovascular events in patients with COPD; however, these were not modelled explicitly. The justification provided was that only a small number of events were observed, with no meaningful difference between treatment arms, and therefore they were not considered a significant driver of model results. This was presented as a conservative assumption by the Company.

COPD management costs

The COPD management resources were assumed to be independent of health state and were sourced from the economic model developed for NICE NG115.¹ These were derived by weighting the frequency of resource use by the proportion of patients in each GOLD severity group and then adjusting the resulting values to reflect the 3-month model cycle. The cost of resources used were calculated by applying respective unit costs (Table 4:15).

Table 4:15: COPD management costs applied in the Company's base-case economic model

Resources	Cost per unit (£)	Frequency per cycle	Source for cost	Source of frequency data-NG115 ¹
GP visit	45.00	0.34	Unit cost for a GP, Cost per surgery consultation lasting 10 mins (including qualifications and direct care staff costs); unit costs of health and social care ¹⁰⁶	NG115-Committee consensus

Resources	Cost per unit (£)	Frequency per cycle	Source for cost	Source of frequency data-NG115 ¹
Respiratory team visit	289.00	0.35	Episode assumed to comprise six 40-minute visits from either a band 6 (75%) or band 7 (25%) PSSRU 2023/24 hospital nurse ¹⁰⁶	NG115-Committee consensus
Outpatient visit	204.98	0.18	NHS reference costs 2023/24 ¹⁰⁷ – weighted average of Respiratory services, Outpatient attendances (340 and 341) ¹⁰⁷	NG115-Committee consensus
Spirometry	37.84	0.43	NHS Reference Costs 2010/2011, outpatient spirometry and bronchodilator response test – inflated to 2023/34 using the PSSRU inflation indices ¹⁰	NG115-Committee consensus
Pulmonary rehabilitation	158.78	0.01	NHS Reference Costs 2023/24 ¹⁰⁷ – weighted average of pulmonary rehabilitation service outpatient procedures ¹⁰⁷	NG115-Price et al, 2013
Oral corticosteroids	0.49	0.38	GlobalData 2025 ¹⁰⁸	NG115-Price et al, 2013
Home oxygen therapy (proportion of patients)	19.33	0.02	Hertel <i>et al.</i> , 2012 ¹⁰⁹ – inflated to 2023/24 using the PSSRU inflation indices ¹⁰⁶	NG115-Price et al, 2013
Influenza vaccine (proportion of patients)	13.50	0.18	GlobalData 2025 ¹⁰⁸	NG115-Price et al, 2013
CT scan	102.84	0.01	NHS Reference Costs 2023/24 – Directly accessed CT scans - Diagnostic Imaging Service, excluding 18 years and under (RD20A) ¹⁰⁷	NG115-Committee consensus
Total costs per model cycle (£)	176.16			
Abbreviations: COPD = chronic obstructive pulmonary disease; CT = computerised tomography; GP = general practitioner; PSSRU = Personal Social Services Research Unit. Source: CS, Table 65 ⁶ and NG115 economic model ¹				

EAG Comment: The EAG understands that the Company's decision to exclude the cardiovascular events from the economic model was based on the small number of events observed in the clinical evidence base and the absence of meaningful differences between treatment arms. However, the

EAG initially considered this justification to be insufficient, given that cardiovascular events in patients with COPD are typically associated with substantial costs and impact on HRQoL. Consequently, the assumption of no differential treatment effect could potentially underestimate the influence of cardiovascular events on the cost-effectiveness results. At the PfC,¹² the EAG requested that the Company provide the cardiovascular event data across the trial arms, together with the observed differences. The data subsequently provided by the Company (in response B9)¹² aligned with its original justification for excluding cardiovascular events demonstrating no meaningful differences between treatment arms.

The EAG considers the Company's approach to estimating the frequency of health state resource use for COPD management to be methodologically appropriate. However, the EAG notes that in the NG115 economic model,¹ several of the underlying resource use inputs were derived from NICE committee consensus rather than empirical data, which may introduce additional uncertainty into these estimates. Nevertheless, given the limited availability of robust evidence, the EAG considers the Company's use of NICE committee derived inputs to be reasonable and pragmatic approach.

In addition, at the PfC,¹² the EAG asked the Company to check the accuracy of the unit cost for an outpatient visit (£204.98) used in its submission. The EAG's calculations indicated a lower unit cost of outpatient visit (£189.50). In its response (B6),¹² it was clear that the discrepancy in the unit costs arose because the Company had considered only consultant-led costs in its unit cost estimates. Nevertheless, the Company conducted a scenario analysis using the EAG provided unit costs for an outpatient visit, which had a negligible impact on the results of the Company's base-case model (see Section 4.3.2.3, Scenario 26, Table 4:29 and Table 4:30).

Exacerbation costs

The frequencies of resource use associated with moderate exacerbations were also informed by the NG115 economic model,¹ where estimates were

based on the committee consensus due to the absence of empirical evidence (Table 4:16). The Company applied the resource use associated with non-hospitalised exacerbations reported in the NG115 economic model¹ to represent resource utilisation in moderate exacerbations. However, the Company made minor amendments to the General Practitioner (GP) visit frequency and the use of oral corticosteroids, for which no rationale was provided in CS, though the EAG does not find these tiny differences to have any meaningful impact in the cost-effectiveness results.

Table 4:16: Moderate exacerbation resource use costs used in the Company's economic model

Resources	Cost per unit (£)	Frequency per event	Source for cost
A&E visit without admission	123.75	0.30	NHS reference costs 2023/24 ¹⁰⁷ – Emergency Medicine, weighted average of Emergency Medicine, No investigation with No Significant Treatment (VB11Z) ¹⁰⁷
Respiratory team visit	289.00	0.10	Episode assumed to comprise six 40-minute visits from either a band 6 (75%) or band 7 (25%) PSSRU 2023/24 ^{1,106}
GP Visit	45.00	1.00	Unit cost for a GP, cost per surgery consultation lasting 10 mins (including qualifications and direct care staff costs) – unit costs of health and social care ¹⁰⁶
OCS (number of prescriptions)	0.49	0.00	GlobalData 2025 ¹⁰⁸
Antibiotics (number of prescriptions)	5.00	0.07	GlobalData 2025 ¹⁰⁸
Total costs per model cycle (£)	121.52		
Abbreviations: A&E = accident and emergency; GP = general practitioner; OCS = oral corticosteroids; PSSRU = personal social services research unit. Source: CS, Table 66 ⁶			

Severe exacerbations

The Company used the frequency of resource use for severe exacerbations (

Table 4:17) from the dupilumab NICE submission,²⁵ which was based on an analysis of Hospital Episode Statistics (HES) resource-utilisation data from 2018-2024,¹¹⁰ to estimate resource use for severe exacerbations. It was assumed that severe exacerbations would require a hospital stay. The Company did not include the cost of follow-up outpatient appointments within 30 days in their analysis; this followed the EAG's preferred analysis based in the dupilumab NICE submission.¹⁸ Resource use costs were applied per severe exacerbation event in the model. The Company made a conservative assumption that the frequencies and costs for frequent severe exacerbations were equivalent to those of severe exacerbations, due to the absence of granular data. However, the Company acknowledges that this assumption may underestimate the true economic burden, as subsequent exacerbations could be more severe and more resource intensive.

Table 4:17: Severe exacerbation resource use and costs used in the Company's base-case economic model

Resources	Cost per unit (£)	Frequency per event	Source for cost
Ambulance transport	250.02	70.00%	NHS reference costs 2023/24 ¹⁰⁷ – weighted average of ambulance codes
A&E admission	353.92	88.00%	NHS reference costs 2023/24 ¹⁰⁷ – weighted average of Emergency Medicine, Category 1 Investigation with Category 3-4 treatment codes (VB06Z)
Hospital LOS	3,350.49	1 day	NHS Reference Costs 2023/24 ¹⁰⁷ – weighted average of COPD nonelective long stay, excluding one day or less category
ICU LOS	2,436.67	1.00%	NHS Reference Costs 2023/24 ¹⁰⁷ – weighted average of all non-specific, general adult critical care bed days
Readmission within 30 days	3,350.49	14.00%	Assumption, same as hospital stay (LOS)
Ventilation	1,071.02	7.00%	NHS Reference Costs 2023/24 ¹⁰⁷ – nonelective, non-invasive ventilation, 19 years and over (short-stay and long-stay)
Oxygen therapy	309.05	2.00%	NHS Reference Costs 2023/24 ¹⁰⁷ – nonelective oxygen assessment and monitoring (non-elective short stay)
CT scan	102.84	10.00%	NHS Reference Costs 2023/24 ¹⁰⁷ – Directly accessed CT scans – Diagnostic Imaging Service, excluding 18 years and under (RD20A)
Echocardiogram	137.49	5.00%	NHS Reference Costs 2023/24 ¹⁰⁷ – directly accessed simple echocardiograms, 19 years and over (Diagnostic Imaging Services)
CPAP therapy	1,071.02	1.00%	Assumption, same as ventilation
Follow-up outpatient appointments within 90 days of exacerbation	204.98	37.00%	NHS reference costs 2023/24 ¹⁰⁷ – weighted average of Respiratory services, Outpatient attendances (340 and 341)
Total costs per model cycle (£)	4,515.26		
Abbreviations: A&E = accident and emergency; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airway pressure; CT = computerised tomography; ICU = intensive care unit; LOS = length of stay. Source: CS, Table 67 ⁶			

EAG comment: The EAG accepts the Company's use of the NG115 economic model¹ as the source for the resource use estimates in moderate exacerbations as a reasonable and pragmatic approach, given the absence of empirical data. However, several of the NG115¹ resource utilisation estimates are based on committee consensus rather than observed evidence, and therefore could introduce additional uncertainty in these data, which the Company does not acknowledge in their submission. At the PfC,¹² the EAG asked the Company to confirm the correctness of some of the parameters (frequency of oral corticosteroids (OCS) use reported for moderate exacerbation management, the costs of OCS, influenza vaccine and antibiotics) used to generate moderate exacerbation resource use costs. Some minor reporting errors were identified (corrected errors were frequency per event of OCS prescription=1, and per event antibiotics=2). The Company stated (in its response B6)¹² that other estimates of cost of OCS, antibiotic and influenza vaccine were correct at the time they were sourced initially, however these costs changed over time, therefore the Company conducted a scenario analysis using the updated costs (cost of OCS=£0.80; Antibiotic=£0.70, and influenza vaccine=£17.55), which had little impact on the Company base-case results (see Section 4.3.2.3, Scenario 27, Table 4:29 and Table 4:30).

The EAG considers the use of HES informed resource utilisation data from a prior NICE submission for severe exacerbations to be reasonable and generally appropriate. However, the EAG raises concerns that the HES data span years affected by COVID-19, which may distort hospital admission and length of stay data. Furthermore, the assumption of equivalent resource use for severe and frequent severe exacerbations may underestimate the true economic burden, as resource use is likely to increase with severity and frequency of exacerbations. Nevertheless, the EAG acknowledges the absence of granular data on resource utilisation.

AEs and related resource-use costs

The Company did not explicitly model AEs or their impact on resource utilisation. Instead, the Company assumed that the frequency and the AEs would be similar between model arms and therefore would not influence the model outcomes.

EAG comment: The EAG finds the assumption of equivalent AE rates reasonable. AEs observed in safety populations of the MATINEE, METREX and METREO trials were similar between mepolizumab and placebo (see Section 2.11, CS).⁶ The EAG therefore does not expect exclusion of AEs from the model to affect the cost-effectiveness results.

Miscellaneous costs and resource use

The Company explored the inclusion of additional indirect costs (costs associated with productivity loss and early retirement) in scenario analysis; these costs were not modelled in the base-case analysis. Caregiver burden was not modelled due to the lack of evidence.

Productivity loss

The Company's model inputs for productivity loss calculation are summarised in Table 4:18. Productivity days lost per month were calculated by weighting estimates reported in Jansson et al. 2013¹¹¹ by the proportion of patients in each GOLD severity category from the pooled mepolizumab trial data analysis and subsequently deriving the number of productivity days lost per model cycle. The model also included additional days lost due to exacerbations. For moderate exacerbations, half a day was assumed to be lost to account for a patient's GP visit and was multiplied by the mean number of moderate exacerbations (■). For severe and frequent severe exacerbations, 5.25 days were assumed to be lost and were multiplied by the mean number of severe exacerbations (■). These exacerbation events were sourced from the year prior to randomisation in the pooled trials.

Finally, the cost of lost productivity was calculated for patients below the retirement age and was applied as the product of days lost per model cycle and the average salary per day in the UK. The Company estimated the proportion of patients under the retirement age in each model cycle by assuming a normal distribution around the mean retirement age used in the Markov model.

Table 4:18: Company's model inputs for productivity loss

Parameter	Unit value	Source
Retirement age (years) (mean (SD))	66 (4)	ONS milestones ¹¹²
Employment rate (%)	77.86	ONS A04: Summary of employment, unemployment and economic inactivity for people below state pension age 2025 ¹¹³
Average annual salary (£)	37,430	ONS employee earnings in the UK 2024 ¹¹⁴
Number of working days in a year	256	Assumption
Productivity days lost per cycle (baseline)	2.15	Jansson <i>et al.</i> , 2013 ¹¹¹
Days lost per moderate exacerbation event	■	Half day multiplied by average moderate exacerbations year prior to randomisation (■), adjusted for 3-month model cycle length
Days lost per severe exacerbation event	■	5.25 days multiplied by average moderate exacerbations year prior to randomisation (■), adjusted for 3-month model cycle length
Abbreviations: ONS = Office for National Statistics; SD = standard deviation. Source: CS, Table 68 ⁶		

Early retirement

The Company's model inputs for early retirement loss are summarised in Table 4:19. The cost of early retirement was calculated by weighting the proportions of patients retiring early due to COPD, as reported in Wacker *et al.* 2016,¹¹⁵ by the proportion of patients in each GOLD severity category from the pooled trial data. This was then multiplied by the number of days in each model cycle and the average salary per day. The Company did not assume

any retirement loss resulting from exacerbation events and applied the total costs to each health state for both treatments.

Table 4:19: Company's model inputs for early retirement loss

Parameter	Unit value	Source
Weighted early retirement (%)	33.3	Wacker <i>et al.</i> , 2016 ¹¹⁵ and pooled trial analysis
Early retirement in the general population (%)	14.7	Wacker <i>et al.</i> , 2016 ¹¹⁵
Excess early retirement for patients with COPD (%)	18.6	Calculated
Total cost per cycle for an early retirement (£)	1,736	
Abbreviations: COPD = chronic obstructive pulmonary disease. Source: CS, Table 69 ⁶		

EAG Comment: The EAG considers the Company's approach to estimate the early retirement costs reasonable, however, reliance on a single data source may bias estimates.

The EAG notes that estimating the proportion of patients below the retirement age in each model cycle by assuming a normal distribution around the mean retirement age, based on the cohort's mean age, is potentially biased. As a result, the proportion of patients assumed to be of working age in each cycle may be overestimated, leading to an overestimation of productivity loss costs in the model. The EAG considers that the Company's approach is perhaps overly simplistic for a cohort Markov model. A more appropriate and robust approach would have been to estimate the proportion of patients below retirement age for each model cycle explicitly and apply productivity losses accordingly. At the PfC,¹² the EAG sought clarification on this issue. In response (B7),¹² the Company justified its approach as being consistent with that used in a previous NICE submission.¹⁸ However, the EAG does not agree that this justifies the methodological choice. Nevertheless, productivity losses were included only in an additional scenario adopting a societal perspective, which lies outside the NICE recommended NHS and PSS perspective and therefore this issue is unlikely to be a key driver of the decision making.

Regardless of the issue with the approach described above, at the PfC,¹² the EAG sought clarification regarding a potential error in the formula used to calculate indirect costs in the Company's model trace sheets for mepolizumab and dupilumab. In its response (B7),¹² the Company confirmed that the formulas differed from those used in SoC trace sheet (because the SoC trace sheet did not include events on discontinuation) and stated that the formula were correctly implemented. However, the EAG considers the formulas are missing brackets, which results in incorrect estimates of indirect estimates. An example of the corrected formula applied by the EAG in the trace sheets (in the DM column) is given in the Section 6 (Appendix, p. 231).

The correction to the formula increases the results observed in the Company's scenario analysis adopting a societal perspective, however the ICER (mepolizumab versus SoC) remained below the NICE threshold of £20,000 per QALY (see Section 4.4.2, Scenario 4,

Table 4:32 and Table 4:33). Nevertheless, the corrected formula affects only the calculation of indirect costs and does not impact the Company's base-case results from the NHS and PSS perspective. The EAG maintains the Company's approach to estimating the percentage under retirement in each model cycle is not appropriate.

4.3 Company's cost-effectiveness result

The Company included SoC as the primary comparator for mepolizumab + SoC in patients with uncontrolled COPD patients. As an exploratory analysis, the Company also compared mepolizumab +SoC versus dupilumab + SoC. The results of the MAIC conducted by the Company indicated no significant difference in effectiveness between mepolizumab and dupilumab.⁶ In addition, at the time of CS, the NICE decision on dupilumab as an add-on treatment for COPD was still pending.²⁵ Therefore, the Company submitted a cost-utility analysis. However, given the lack of evidence of a difference in clinical effectiveness between mepolizumab and dupilumab, the Company also submitted a cost-minimisation analysis comparing the costs of mepolizumab against dupilumab. The EAG only appraised the cost-utility analysis for this submission.

4.3.1 Company base-case

The Company's base-case cost-utility analysis used list prices for SoC and dupilumab, whereas the PAS discounted price was used for mepolizumab. Table 4:20 presents the Company's base-case deterministic incremental results for mepolizumab + SoC compared with SoC alone and with dupilumab + SoC. In the incremental analysis, mepolizumab + SoC incurred an additional cost of [REDACTED] and generated [REDACTED] additional QALYs compared with SoC. The ICER for mepolizumab +SoC versus SoC was £18,347 per QALY gained, which is below the NICE willingness-to-pay threshold of £20,000-£30,000 per QALY. Mepolizumab + SoC dominated dupilumab + SoC in the cost-effectiveness analysis being both less costly and more effective in the base-case analysis.

The net health benefit and net monetary benefit from treatments at willingness-to-pay thresholds of £20,000 and £30,000 are presented in Table 4:21.

Table 4:20: Deterministic Company's base-case incremental analysis

Treatment	Total			Incremental			ICER versus SoC	ICER versus Mepolizumab	Fully incremental ICER
	costs	LYG	QALY	costs	LYG	QALY			
SoC	████	██	██	-	-	-	-	-	-
Mepolizumab + SoC	████	██	██	████	██	██	£18,347	-	£18,347
Dupilumab + SoC	████	██	██	████	██	██	£120,738	Dominated	Dominated

Source: CS document, Section 3.11.1, Table 72⁶
Abbreviations: ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years; SoC = standard of care.

Table 4:21: Deterministic Company's base-case NHB and NMB

Treatment	NHB 20k (mepolizumab versus comp)	NHB 30k (mepolizumab versus comp)	NMB 20k (mepolizumab versus comp)	NMB 30k (mepolizumab versus comp)
SoC	0.07	0.35	£62,788	£105,320
Mepolizumab + SoC	-	-	£64,286	£115,883
Dupilumab + SoC	3.47	2.39	-£5,184	£44,095

Source: CS document, Section 3.10.1, Table 72, Company's economic model^{6, 97}
Abbreviations: NHB = net health benefit; NMB = net monetary benefit; SoC = standard of care.

EAG Comment: The EAG considers that the deterministic analysis conducted by the Company is broadly consistent with the NICE reference case and has been appropriately undertaken. In the treatment of patients with COPD, the results indicate that mepolizumab + SoC is likely to be cost-effective within the NICE threshold of £20,000 per QALY when compared with SoC alone and with dupilumab + SoC.

4.3.2 Company sensitivity and scenario analysis

The Company undertook a range of sensitivity and scenario analysis on the base-case to quantify uncertainty and explore the assumptions underpinning the model.

4.3.2.1 Company's probabilistic sensitivity analysis

A probabilistic sensitivity analysis was conducted on the Company's base-case using 5,000 iterations.⁹⁷ Table 4:22 presents the fully incremental base-case probabilistic results for mepolizumab + SoC compared with SoC alone and with dupilumab + SoC. In the incremental analysis, mepolizumab + SoC was associated with an incremental cost of [REDACTED] and an incremental gain of [REDACTED] QALYs compared with SoC. The resulting ICER for mepolizumab + SoC versus SoC was £18,383 per QALY gained (95% CI: £11,753- £37,926), which is below the NICE willingness-to-pay threshold of £20,000 - £30,000 per QALY. Mepolizumab + SoC dominated dupilumab + SoC in the cost-effectiveness analysis.

Table 4:23 presents the incremental net health benefit (NHB) and incremental net monetary benefit (NMB) results from the probabilistic analysis. The incremental NHB of mepolizumab + SoC compared with SoC alone and dupilumab + SoC were 0.07 and 3.49, respectively, at a £20,000 per QALY threshold. The incremental NMB for mepolizumab + SoC vs SoC was £1,463 at the £20,000 threshold, which was the highest among the treatments evaluated.

Figure 4.2 and

Figure 4.3 depict the cost-effectiveness plane and the cost-effectiveness acceptability curve from the probabilistic sensitivity analysis (PSA). The probability that mepolizumab + SoC is cost-effective was 70.4% and 99.7% at willingness-to-pay threshold of £20,000 and £30,000 per QALY, respectively.

Table 4:22: Company's probabilistic incremental cost-effectiveness result

Treatment	Total			Incremental			ICER versus SoC (95% Cr I)	ICER versus Mepolizumab	Fully incremental ICER
	costs	LYG	QALY	costs	LYG	QALY			
SoC	████	██	██	-	-	-	-	-	-
Mepolizumab + SoC	████	██	██	████	██	██	£18,383 (£11,753- £37,926)	-	£18,383
Dupilumab + SoC	████	██	██	████	██	██	£134,920 (£122,882 - £470,981,219)	Dominated	Dominated

Source: CS document, Section 3.11.1, Table 73⁶
Abbreviations: Cr I = credible interval; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years; SoC = standard of care.

Table 4:23: Company's probabilistic NHB and NMB result

Treatment	NHB at £20K (mepolizumab versus comp)	NHB at £30K (mepolizumab versus comp)	NMB at £20K (mepolizumab versus comp)	NMB at £30K (mepolizumab versus comp)
SoC	0.07	0.35	£1,463	£10,508
Mepolizumab + SoC	-	-	-	-
Dupilumab + SoC	3.49	2.43	£69,755	£72,858

Source: CS document, Section 3.10.1, Table 72, Company economic model^{6, 97}
Abbreviations: NHB = net health benefit; NMB = net monetary benefit; SoC = standard of care.

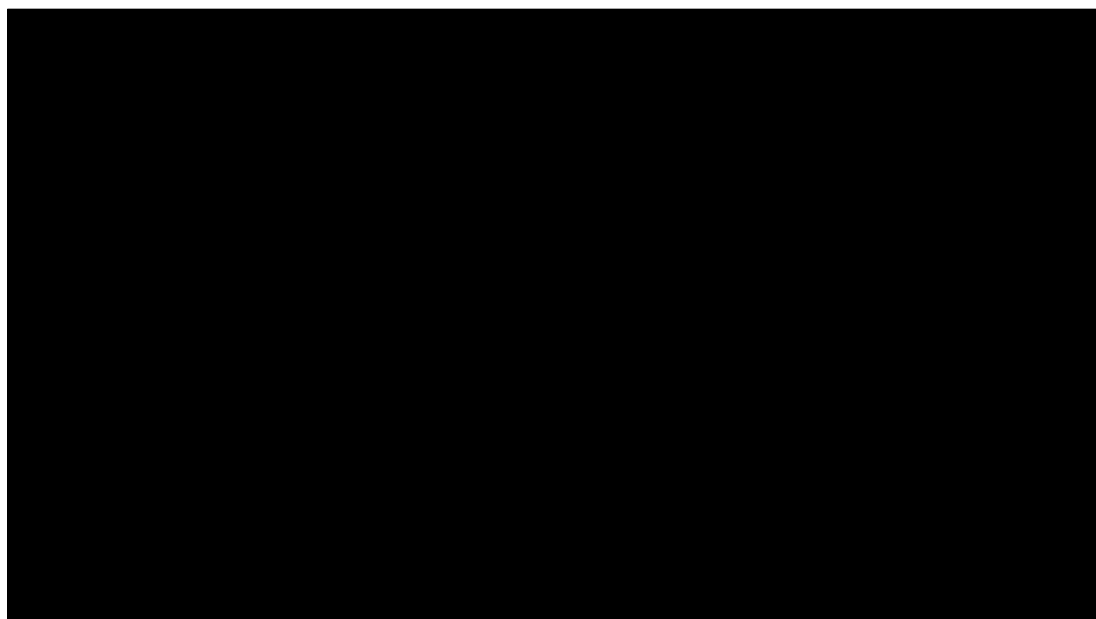
Figure 4.2: Company base-case CE plane



Source: CS economic model⁹⁷

Abbreviations: Dupi, = dupilumab; mepo = mepolizumab; QALY = quality-adjusted life years; SoC = standard of care.

Figure 4.3: Company base-case cost-effectiveness acceptability curve (CEAC)



Source: CS economic model⁹⁷

Abbreviations: CEAC = cost-effectiveness acceptability curve; SoC = standard of care.

EAG Comment: The EAG conducted PSA runs to assess the uncertainty and variability in the incremental results observed in the Company's PSA. The EAG considers the results were robust and stable at 5,000 iterations.

4.3.2.2 Company's deterministic sensitivity analysis

To explore the impact of uncertainty in individual model parameters on the base-case, the Company conducted one-way sensitivity analysis (OWSA). A single parameter was varied, at a time, across the upper and lower bound values of its 95% CI. When 95% CI data was not available, $\pm 10\%$ of the mean value was assumed to estimate the confidence interval.

Table 4:24 and Figure 4.4 present the results of the OWSA for mepolizumab + SoC versus SoC alone. The baseline probability of a first severe exacerbation had the largest impact on the ICER, which ranged from £15,758 to £22,345 per QALY. This was followed by the treatment effect on severe exacerbations versus SoC for responders, with an ICER range from £16,374 to £22,447 per QALY.

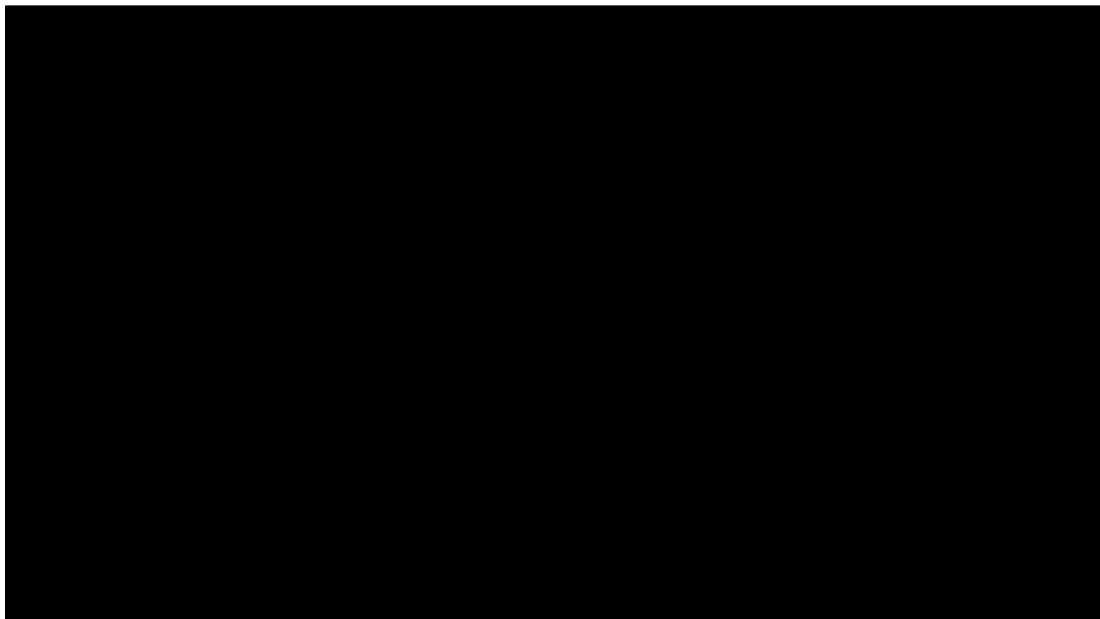
Figure 4.5 presents the tornado diagram of the OWSA results for mepolizumab + Soc versus dupilumab + SoC. The treatment effect on severe exacerbations for mepolizumab + SoC versus dupilumab + SoC had the largest impact on the model results. The Company used NHB as the measure to assess the impact of each parameter in this analysis, since dupilumab (at the list price used in the analysis) was dominated in the base-case analysis.

Table 4:24: Company's one-way sensitivity analysis results, mepolizumab + SoC versus SoC

Parameters	ICER - Upper bound (£/QALY)	ICER - Lower bound (£/QALY)	Difference
Baseline probability of first severe exacerbation (+/-95% CI)	£22,345	£15,758	£6,587
Severe exacerbation treatment effect vs SoC - responders (+/- 95% CI)	£16,374	£22,447	£6,074
HCRU for frequent severe exacerbations	£20,111	£14,818	£5,293
Probability of subsequent severe exacerbations - frequent severe exacerbation health states (+/- 95% CI)	£20,620	£16,061	£4,559
Probability of subsequent severe exacerbations - severe exacerbation health states (+/- 95% CI) Severe exacerbation treatment effect vs SoC (+/-95% CI)	£20,453	£16,599	£3,854
Severe exacerbation treatment effect vs SoC (+/-95% CI)	£17,055	£20,588	£3,533
Probability of subsequent severe exacerbations - moderate exacerbation health states (+/- 95% CI)	£20,431	£16,934	£3,497

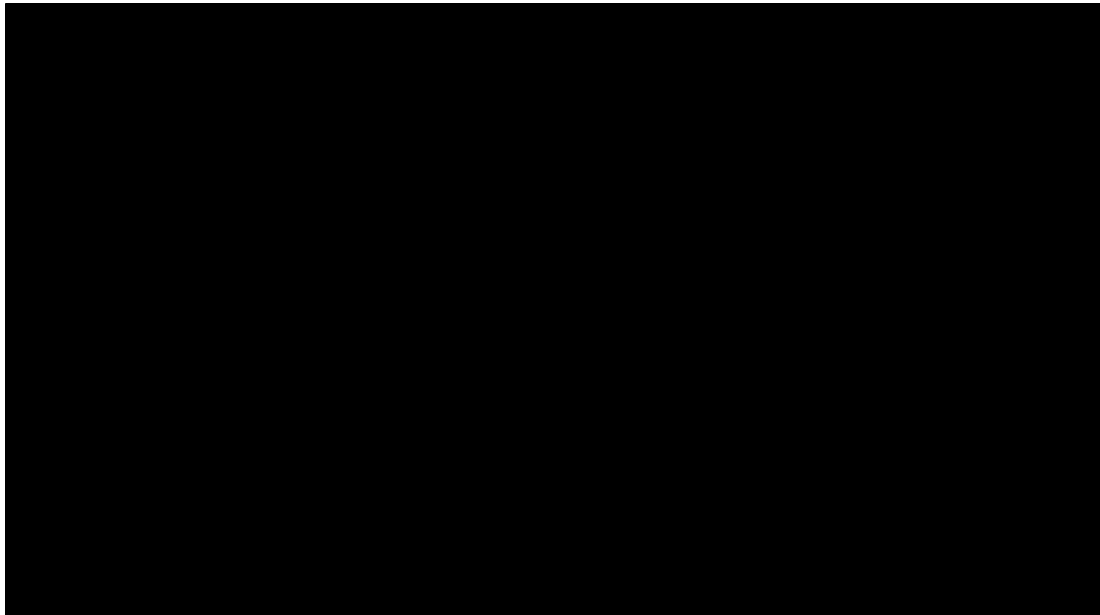
Probability of subsequent severe exacerbations - post severe exacerbation health state (+/-95% CI)	£20,307	£17,278	£3,029
HCRU for severe exacerbations	£19,210	£16,620	£2,590
Case fatality rate, severe and frequent severe	£19,512	£17,715	£1,798
Source: Company economic model ⁹⁷ Abbreviations: CI = confidence interval; HCRU = health care resource use; SoC = standard of care			

Figure 4.4: Tornado diagram illustrating top 10 drivers of variance around the ICERs (mepolizumab + SoC versus SoC)



Source: Company economic model⁹⁷
Abbreviations: CI = confidence interval; dupi = dupilumab; ICER = incremental cost-effectiveness ratio; HCRU = health care resource use; mepo = mepolizumab; QALY = quality-adjusted life years; SoC = standard of care

Figure 4.5: Tornado diagram illustrating top 10 drivers of variance around NHB (mepolizumab + SoC versus dupilumab + SoC)



Source: Company economic model⁹⁷

Abbreviations: CI, confidence interval; dupi = dupilumab; HCRU = health care resource use; mepo = mepolizumab; NHB = net health benefit; QALY = quality-adjusted life years; SoC = standard of care.

EAG Comment: The Company used ICERs to assess the impact of each parameter in the OWSA for mepolizumab + SoC versus SoC alone, however NHB was used for mepolizumab + SoC versus dupilumab + SoC. The EAG considers this approach appropriate, as dupilumab (at the list price used in the analysis) was dominated in the base-case analysis. The EAG notes, however, the difference in reporting the impact across comparisons, and recommends that a caveat should be included to highlight this inconsistency.

4.3.2.3 Company's scenario analysis

The Company explored different scenario analysis using the base-case. Table 4:25 provides details of the various scenarios considered in the model. Table 4:26 presents the results of scenario analyses for mepolizumab + SoC versus SoC alone. Scenarios exploring different time horizons (5 years and 10 years) had the greatest impact on the ICER, exceeding the £20,000 - £30,000 per QALY threshold. All the other scenario results remained below the NICE prescribed ICER threshold.

Table 4:25: Scenarios explored by the Company

No.	Model parameter	Base-case	Scenario
1	Discount rate for costs and outcomes.	3.5%	0%
2			1.5%
3	Time horizon	Lifetime (30 years)	5 years
4			10 years
5	Source of baseline exacerbation rates	The pooled trial analysis (MATINEE, METREX, METREO) including IMPACT, and ECLIPSE	Calibrated to prior year frequency from MATINEE trial.
6			the METREX/ METREO trials.
7	Source of exacerbation rate in Year 1	Pooled mITT-300 analysis	MATINEE trial
8			the pooled mITT-300, split by first and subsequent exacerbation. Subsequent exacerbation rate set equal to first exacerbation rate.
9	Determination of patients with CB, considered in MAIC analysis	By investigator assessment at baseline (preferred approach used in the BOREAS/NOTUS trials to define CB.)	Using responses to the SGRQ-C questionnaire at baseline.
10	Exacerbation rate treatment in Year 2+ for responders	Pooled mITT-300 analysis	MATINEE trial
11	Source of Treatment discontinuation in Year-2+	MATINEE trial for mepolizumab and dupilumab	Real-world evidence (15%).
12			Real-world evidence in year 2+ (15%) for dupilumab and from MATINEE for mepolizumab.
13	SMR	An SMR of 2.5 is applied to background mortality estimates for all health states	No SMR applied to background mortality estimates for all health states
14	CFR applied to severe exacerbation rates	A CFR of 15.6% is applied to severe exacerbation health states	CFR of 14.2% applied to severe exacerbation health states
15	Source of Baseline utility value	Pooled trial analysis including the IMPACT trial	MATINEE trial
16	Disutility associated with each exacerbation state	Pooled trial analysis including the IMPACT trial	Jackson et al., 2024. ¹⁰⁴
17			Hoogendoorn et al., 2011. (from NICE TA461) ¹¹⁶
18			Trial SGRQ responses.

No.	Model parameter	Base-case	Scenario
19			Disutility values associated with each exacerbation state taken from the pooled trial analysis including the IMPACT trial. Post-severe disutility set equal to severe (9-12 months) to prevent implausible outcomes.
20	Age-adjustment for utility values included	age-adjusted included using Hernandez-Alava, 2022	No age adjustment is included.
21	Societal costs	Not included	Productivity loss and early retirement costs included in the model
Source: CS document, Section 3.11.3, Table 74 ⁶ Abbreviations: CFR = case-fatality rate; COPD = chronic obstructive pulmonary disease; OCS = oral corticosteroids; mITT-300 = modified intention-to-treat-300; RR = rate ratio; SMR = standardised mortality ratio			

Table 4:26: Company's scenario analysis results for mepolizumab versus SoC

Scenario	Incremental costs	Incremental QALYs	Pairwise ICER (mepolizumab versus SoC)
Base-case	████	██	£18,347
1	████	██	£16,051
2	████	██	£16,991
3	████	██	£59,897
4	████	██	£26,281
5	████	██	£11,640
6	████	██	£15,403
7	████	██	£17,814
8	████	██	£17,599
10	████	██	£19,756
11	████	██	£18,494
13	████	██	£15,633
14	████	██	£18,615
15	████	██	£18,273
16	████	██	£18,282
17	████	██	£18,352
18	████	██	£18,004
19	████	██	£18,242

Scenario	Incremental costs	Incremental QALYs	Pairwise ICER (mepolizumab versus SoC)
20	████	██	£18,347
21	████	██	£14,866
Source: CS document, Section 3.11.3, Table 74 ⁶ Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years; SoC = standard of care.			

Table 4:27 provides the results of the scenario analyses comparing mepolizumab + SoC versus dupilumab + SoC. In all the scenarios, mepolizumab + SoC was dominant over dupilumab + SoC.

Table 4:27: Company's scenario analysis results for mepolizumab versus dupilumab

Scenario	Incremental costs	Incremental QALYs	ICER (mepolizumab vs. dupilumab)	Incremental NHB (mepolizumab versus dupilumab)
Base-case	████	██	Dominant	2.39
1	████	██	Dominant	2.92
2	████	██	Dominant	2.67
3	████	██	Dominant	1.38
4	████	██	Dominant	2.03
5	████	██	Dominant	2.12
6	████	██	Dominant	2.30
7	████	██	Dominant	2.41
8	████	██	Dominant	2.42
9	████	██	Dominant	2.25
10	████	██	Dominant	2.38
11	████	██	Dominant	1.77
12	████	██	Dominant	1.87
13	████	██	Dominant	2.81
14	████	██	Dominant	2.40
15	████	██	Dominant	2.39
16	████	██	Dominant	2.38
17	████	██	Dominant	2.38
18	████	██	Dominant	2.40

Scenario	Incremental costs	Incremental QALYs	ICER (mepolizumab vs. dupilumab)	Incremental NHB (mepolizumab versus dupilumab)
19	████	██	Dominant	2.39
20	████	██	Dominant	2.39
21	████	██	Dominant	2.39
Source: CS document, Section 3.11.3, Table 74 ⁶ Abbreviations: ICER = incremental cost-effectiveness ratio; NHB = net health benefit; QALY= quality-adjusted life years; SoC = standard of care.				

EAG Comment: The EAG considers the Company’s exploration of parameter uncertainty in the scenario analysis to be appropriate. However, the EAG notes that a caveat should be included to highlight the inconsistency in reporting, as the impact was reported using ICER for mepolizumab + SoC versus SoC alone but using NHB for mepolizumab + SoC versus dupilumab + SoC. This would avoid any potential misinterpretation of these differences in reporting. In addition, the Company reported ICERs in Table 4:26 are not exactly the same as the ones computed using the incremental costs and incremental QALYs reported. The discrepancy is likely to be a result of rounding off the estimates before calculation, however, this was not explicitly flagged by the Company.

Company’s additional scenario analysis

In response to the EAG’s PfC,¹² the Company undertook additional scenario analyses (Table 4:28).

When mepolizumab + SoC was compared with SoC alone, the scenario with higher SMR of 3.85 resulted in an ICER exceeding the £20,000 per QALY threshold. The scenario considering a younger population cohort (40 years) had the largest impact, with an ICER of £66,620, suggesting that mepolizumab + SoC is unlikely to be cost-effective in younger adults. However, all the other scenarios had minimal impact on the ICER relative to the base-case, and the results remained below the NICE threshold (Table 4:29).

When mepolizumab + SoC was compared with dupilumab + SoC, mepolizumab + SoC remained the dominant treatment across all additional scenarios (Table 4:30). The probabilistic results for the scenario—which account for the uncertainty reflected in the wide credible intervals of the ML-NMR rate ratios comparing mepolizumab with dupilumab—were generally consistent with the deterministic estimate. The analysis showed an incremental cost of █████, an incremental QALY gain of █████, and a NHB of 2.44. These findings closely align with the deterministic results reported in Scenario 30, in Table 4:30).

Table 4:28: Company’s additional scenarios after EAG’s PfC¹²

No.	Model parameter	Base-case	Scenario
22	SMR	SMR of 2.50 sourced from Samyshkin et al. 2014 ⁹⁹ for severe COPD was applied	SMR reported in Samyshkin et al. 2014 ⁹⁹ of 3.85 for very severe COPD was applied
23	Age adjustment in CFR	CFR of 14.2% from Samyshkin et al. 2014 ⁹⁹ and the age adjustment method from Hoogendoorn et al. 2011 ¹⁰⁰ was applied	Age dependent CFR from NRAP audit using the age adjustment from Samyshkin et al. 2014 ⁹⁹
24	Dupilumab discontinuation in first year	COVID-related discontinuations applied	COVID-related discontinuations removed
25	Treatment discontinuation	████% discontinuation per cycle beyond year 1 (applied to mepolizumab and dupilumab)	4.58% discontinuation per cycle beyond year 1 (applied to mepolizumab and dupilumab)
26	Outpatient costs	Company calculated cost - £204.98	EAG calculated cost - £189.50
27	Cost of oral corticosteroids, influenza vaccine use and antibiotic use in moderated exacerbation management	OCS - £0.49 per pack for prednisolone 5 mg, Antibiotics - Amoxicillin 250 mg capsules of £5.00 per pack, Influenza vaccine - £13.50	OCS - £0.80 per pack for prednisolone 5 mg, Antibiotics - Amoxicillin 250 mg capsules of £0.70 per pack, Influenza vaccine - £17.55
28	Treatment effectiveness based on age of patients	the Rate Ratio (RR) for moderate/severe exacerbations, 0.84, for mean age 65.4	the Rate Ratio (RR) for moderate/ severe exacerbations, 0.93, in the age group 40-64 years from mITT-300 population,

		years from pooled mITT-300	and other parameters available for this younger age group
29	Disutility associated with Frequent severe (9-12 months)	The disutility of [REDACTED] was applied to Frequent severe (9-12 months) health state	Disutility in the frequent severe (9–12 months) state is set equal to that of the frequent severe (6-9 months) state ([REDACTED]).
30	Rate ratios (mepolizumab vs dupilumab) of moderate or severe exacerbations estimated from ML-NMR	Rate ratios (mepolizumab vs dupilumab) of moderate or severe exacerbations from MAIC	Updated rate ratios based on ML-NMR used in both the deterministic and probabilistic analysis
Source: Points for Clarification response ¹² Abbreviations: CFR = case-fatality rate; COPD = chronic obstructive pulmonary disease; COVID = Coronavirus disease; OCS = oral corticosteroids; mITT-300 = modified intention-to-treat-300; RR = rate ratio; SMR = standardised mortality ratio			

Table 4:29: Company' additional scenario results for mepolizumab versus SoC

Scenario	Incremental costs	Incremental QALYs	Pairwise ICER (mepolizumab vs. SoC)
Base-case	[REDACTED]	[REDACTED]	£18,347
22	[REDACTED]	[REDACTED]	£20,807
23	[REDACTED]	[REDACTED]	£18,661
24	[REDACTED]	[REDACTED]	£18,347
25	[REDACTED]	[REDACTED]	£18,645
26	[REDACTED]	[REDACTED]	£18,338
27	[REDACTED]	[REDACTED]	£18,355
28	[REDACTED]	[REDACTED]	£66,620
29	[REDACTED]	[REDACTED]	£18,318
Source: Clarification response ¹² Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years; SoC = standard of care.			

Table 4:30: Company's additional scenario results for mepolizumab versus dupilumab

Scenario	Incremental costs	Incremental QALYs	ICER (mepolizumab versus dupilumab)	Incremental NHB (mepolizumab versus dupilumab) @30k
Base-case	[REDACTED]	[REDACTED]	Dominant	2.39

Scenario	Incremental costs	Incremental QALYs	ICER (mepolizumab versus dupilumab)	Incremental NHB (mepolizumab versus dupilumab) @30k
22	██████	██	Dominant	2.14
23	██████	██	Dominant	2.38
24	██████	██	Dominant	2.41
25	██████	██	Dominant	1.60
26	██████	██	Dominant	2.39
27	██████	██	Dominant	2.39
28	██████	██	Dominant	3.07
29	██████	██	Dominant	2.39
30	██████	██	Dominant	2.39
Source: Clarification response ¹² Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefits; QALY, quality-adjusted life years				

4.3.3 Model validation and face validity check

The Company outlined the technical (by senior analyst not involved in the original model) and external validation (by clinicians) of their economic model.

EAG comment: The EAG conducted validation and face validity checks of the Company's economic model to ensure that it appropriately reflected the decision problem. The assessment included a review of the model structure, input parameters and assumptions made in the absence of data. A few inconsistencies were identified in the report and model, which were addressed following EAG requests for clarification, although these corrections had negligible impact on the results. An error in the calculation of indirect costs was also identified and corrected by the EAG, and the results are presented as a scenario analysis below. Overall, the EAG considers that the Company's model is valid and robust to assess the cost-effectiveness of mepolizumab + SoC versus SoC alone, and dupilumab + SoC, despite some parameter uncertainties.

4.4 EAG's additional analyses

4.4.1 EAG's preferred assumptions

The EAG considers that the Company's base-case economic model and analysis are appropriate and do not require modifications. Remaining parameter uncertainties raised by the EAG in the PfC were assessed by the Company in the additional scenario analyses presented in Section 4.3.2. Therefore, the EAG agrees with the Company's base-case analysis and has not defined and reported a separate set of EAG preferred assumptions for the purpose of this assessment. However, the EAG has explored the impact of additional parameter uncertainties, which are presented below.

4.4.2 Additional scenario analyses conducted by the EAG

As noted above in Section 4.4.1, the majority of EAG identified parameter uncertainties that required further exploration in scenario analyses were conducted by the Company in response to the PfC. The additional scenario analysis on the Company's base-case conducted by the EAG are reported in Table 4:31.

Table 4:31: Additional scenario analyses conducted by the EAG

No.	Model parameter	Base-case	Scenario
1	General population mortality	Used national life tables for England and Wales (2018-2020) ¹⁶	Using national life tables for England and Wales (2022-2024) ¹⁷
2	Relative risk of mortality for people who discontinue the treatment versus those who do not	Assume a relative risk of 1.	Assuming those who discontinue the treatment will have 10% higher risk of mortality
3	Treatment discontinuation	The annualised discontinuation rate observed over the second year of the MATINEE trial (■■■■) was scaled to a per cycle probability of discontinuation (■■■■) and was used in the model for mepolizumab and dupilumab from Year 2 onwards.	Upper bound (25.8%) of annual discontinuation for mepolizumab and dupilumab for Year 2 onwards in the model.

No.	Model parameter	Base-case	Scenario
		Alternatively, Lower bound (15%) of annual discontinuation (range of estimates from the real world between 15% to 25.8%) from the NICE dupilumab submission ¹⁸ was explored as a scenario for mepolizumab and dupilumab for Year 2 onwards in the model.	
4	Indirect costs (only for societal perspective)	Error in the formula used to calculate the indirect costs in the Company's model trace sheets	Error in formula corrected, but with the Company's retirement percentages

The results of the additional EAG scenarios are presented in

Table 4:32 and Table 4:33. These scenarios did not result in material difference to the ICER observed in the Company base-case analysis. The correction of the error in calculating the indirect costs for the exploratory societal perspective, however increased the ICER (mepolizumab+ SoC versus SoC) to £18,870 (

Table 4:32) from £14,866 presented in the Company's scenario analysis but remains below the £20,000 NICE threshold (Table 4:26). Furthermore, the correction did not have a material difference on the incremental costs for mepolizumab + SoC versus dupilumab + SoC), as it only increased from [REDACTED] (Table 4:27) in the Company's scenario analysis to [REDACTED] (Table 4:33).

Table 4:32: EAG's additional scenario results (mepolizumab + SoC versus SoC)

EAG Scenario	Incremental costs	Incremental QALYs	ICER (mepolizumab versus SoC)
Company Base-case	██████	████	£18,347
1	██████	████	£18,185
2	██████	████	£19,199
3	██████	████	£18,984
4	██████	████	£18,870
Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years; SoC = standard of care.			

Table 4:33: EAG's additional scenario results (mepolizumab + SoC versus dupilumab + SoC)

Scenario	Incremental costs	Incremental QALYs	ICER (mepolizumab versus dupilumab)	Incremental NHB (mepolizumab versus dupilumab) @30k
Company base-case	██████	████	Dominant	2.39
1	██████	████	Dominant	2.41
2	██████	████	Dominant	2.39
3	██████	████	Dominant	1.37
4	██████	████	Dominant	2.39
Abbreviations: ICER = incremental cost-effectiveness ratio; NHB = net health benefits; QALY = quality-adjusted life years.				

4.5 Conclusions of the cost-effectiveness section

In general, the EAG considers the Company's evidence on cost-effectiveness adheres to the NICE decision problem and aligns with the NHS reference case. The decision model structure reflected the impact of COPD exacerbations on health resource utilisation and health related quality of life with the best evidence currently available. The modelled population characteristics including the mean age (65.4 years) were representative of the UK COPD population. Both model structure and population characteristics were validated by the clinical expert consulted by the EAG. Mepolizumab as

an add on treatment regimen, with triple inhaled therapy ICS, LABA and LAMA as comparators, was considered appropriate and was also validated by the clinical expert. The EAG agreed with the Company exploring dupilumab (given the uncertainty and limitations in dupilumab parameters) as a comparator against mepolizumab, and the exclusion of roflumilast and azithromycin (not commonly used in the UK) as comparators, in line with clinical expert opinion. Overall, the EAG considered the Company base-case economic model structure and analysis were appropriate and did not require modifications. Therefore, the EAG did not define an additional or separate EAG base-case, instead the EAG conducted additional exploratory analysis on the Company base-case economic model and analysis.

As discussed in Sections 4.3.2 and 4.4.2, scenario analysis (including those reported in the Company submission, those requested at the PfC, and those undertaken by the EAG) exploring the impact of uncertainty in economic model parameters did not demonstrate any material impact on the observed ICER in the Company base-case results. In most of the scenarios assessed, the ICER remained below the NICE willingness-to-pay threshold of £20,000 per QALY; in some scenarios, the ICER exceeded the £20,000 threshold but remained well below the upper NICE willingness-to-pay threshold of £30,000 per QALY gained. However, the scenario analysis undertaken in the younger population (40-64 years) had a substantial impact on the ICER, with it being more than three times the ICER observed in the Company's base-case analysis. Nevertheless, the EAG acknowledges that the COPD patient population is predominantly observed in clinical practice as above 65 years of age in the UK. Hence, the ICER observed in the younger population group is not representative of the observed UK COPD population (which was also validated by the EAG clinical expert). Therefore, this analysis was considered as exploratory only for the purpose of this assessment.

COPD exacerbation rates were the key drivers of the ICER in the model. However, due to limitations in the available data, uncertainty remains around subsequent exacerbations, long-term exacerbation rates, health care resource

utilisation costs and mortality associated with frequent severe exacerbations, and treatment discontinuation rates beyond 2 years.

Mepolizumab may offer positive incremental net health benefits compared with dupilumab. However, the cost-utility analysis of mepolizumab versus dupilumab was conducted only as an exploratory analysis; the EAG acknowledges the lack of head-to-head trials informing comparative treatment effects, and the uncertainties around model parameters arising from differences in population characteristics between the two treatments. Nevertheless, the additional cost-comparison analysis submitted by the Company showed that mepolizumab would be a cost saving intervention compared with dupilumab.

Considering the limitations discussed above, the EAG has reached the conclusion that mepolizumab is likely to have an ICER below the NICE willingness-to-pay threshold of £20,000 per QALY gained as a treatment option for the UK COPD population.

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6 Appendix

An example of the corrected formula applied by the EAG in the trace sheets (in the DM column) is as follows:

```
IF(perspective=1, 0,H19*(  
  (AVERAGE(AO19:AO20) + AVERAGE(BB19:BB20)) * ic.maintenance.noexac +  
    (AVERAGE(AP19:AP20) + AVERAGE(BC19:BC20)) * ic.maintenance.mod.exac +  
    (AVERAGE(AQ19:AQ20) + AVERAGE(BD19:BD20)) * ic.maintenance.mod3.exac +  
    (AVERAGE(AR19:AS19) + AVERAGE(AR20:AS20) + AVERAGE(BE19:BF19) +  
    AVERAGE(BE20:BF20)) * ic.maintenance.severe1.6m +  
    (AVERAGE(AT19:AU19) + AVERAGE(AT20:AU20) + AVERAGE(BG19:BH19) +  
    AVERAGE(BG20:BH20)) * ic.maintenance.severe1.12m +  
    (AVERAGE(AV19:AW19) + AVERAGE(AV20:AW20) + AVERAGE(BI19:BJ19) +  
    AVERAGE(BI20:BJ20)) * ic.maintenance.severe2.6m +  
    (AVERAGE(AX19:AY19) + AVERAGE(AX20:AY20) + AVERAGE(BK19:BL19) +  
    AVERAGE(BK20:BL20)) * ic.maintenance.severe2.12m +  
    (AVERAGE(AZ19:AZ20) + AVERAGE(BM19:BM20)) * ic.maintenance.post.severe)  
)
```

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

EAG Addendum

Produced by Newcastle University
Authors Louise Tanner, Research Associate
Nawaraj Bhattarai, Senior Research Associate
Sonia Garcia Gonzalez-Moral, Research Associate
Lakshmi Jayachandran, Research Associate
Sheila A Wallace, Research Fellow
Kate Lanyi, Research Associate
Julia Whitehall, Research Associate
Oleta Williams, Research Assistant
Ryan PW Kenny, Senior Research Associate
Asra Asgharzadeh, Senior Research Associate
Gurdeep S Sagoo, Senior Lecturer
Gill Norman, Principal Research Associate
Katie H Thomson, Senior Research Associate

Correspondence to Katie Thomson, Newcastle University
Population Health Sciences Institute,
The Catalyst, Room 3.12, 3 Science Square
Newcastle Helix, Newcastle upon Tyne, NE4 5TG

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Report key:

[REDACTED]

[REDACTED]

NICE additional scenario requests

NICE asked the EAG to review whether the mepolizumab model should use a combined moderate/severe exacerbation rate ratio (RR) (consistent with the dupilumab appraisal) instead of separate RRs for moderate and severe exacerbations. They also asked whether this issue was considered during the EAGs evidence critique and, if so, why it was not reported as a concern. Finally, they asked the EAG to assess whether there are any evidence or modelling differences to the dupilumab appraisal [ID6235] that would justify a different approach.

EAG response:

The primary outcome in the MATINEE, METREO and METREX clinical trials was the annualised rate of moderate/severe exacerbations (combined).

The company in this appraisal used a Markov model with 13 health states characterised by exacerbation severity and time since exacerbation. An additional 12 health states were included to represent patients who discontinued treatment, mirroring the main health states.¹ In comparison, in the dupilumab NICE appraisal [ID6235],² a Markov model with 13 health states characterised by COPD GOLD severity stage and exacerbation status was used (see Table 44 in the company submission (CS)).¹

In the economic model for this appraisal, the treatment effects for mepolizumab versus standard of care were estimated by applying separate RR for moderate and severe exacerbations. However, in the mepolizumab versus dupilumab model, a composite RR of moderate/severe exacerbations is used alongside the severe exacerbation rate alone.

The EAG also notes that the RR values for moderate and severe exacerbations were similar (mepolizumab + SoC versus SoC alone) (Table 1). The impact on the incremental cost-effectiveness ratio (ICER) for using the same RRs (■■■■) had no material impact (Table 2). However, in the scenario analysis where RR = 1 was considered, this gave rise to an ICER slightly over the £20,000 threshold (£20,045).

Table 1: Treatment effect for exacerbation rates, mepolizumab versus background therapy (base case)

Exacerbation type	Rate for moderate exacerbation (95% CI)	Rate for severe exacerbation (95% CI)
Pooled mITT-300 population	██████████	██████████
Source: Table 52 in the CS ¹ Abbreviations: CI, Confidence interval; mITT-300, modified intention-to-treat 300 (participants with BEC ≥300 cells/μL at screening who received ≥1 dose of study treatment and were on triple inhaled therapy [ICS+LABA+LAMA] at baseline.		

Table 2: EAG's additional scenario results (mepolizumab + SoC versus SoC)

Scenario	Incremental costs	Incremental QALYs	ICER (mepolizumab + SoC versus SoC alone)
Company base-case	██████	████	£18,347
RR for severe exacerbation equal to the RR for moderate exacerbation	██████	████	£18,596
RR=1 for severe exacerbations	██████	████	£20,045
Source: Modified from Table 4.32 in EAG report ³ Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years; SoC = standard of care; RR = rate ratio.			

The RR using the matching adjusted indirect comparison (MAIC) estimates of mepolizumab versus dupilumab were 0.91 and 0.68 for moderate/severe and severe respectively (Table 3).

Table 3: Treatment effect for exacerbation rates, mepolizumab versus dupilumab

Exacerbation type	RR for moderate/severe exacerbation (95% CI)	RR for severe exacerbation (95% CI)
Mepolizumab vs. dupilumab	0.91 (0.60, 1.37)	0.68 (0.27, 1.72)
Source: Table 54 in the company submission ¹ Abbreviations: CI = confidence interval; RR = rate ratio.		

In our original critique, we considered that using composite RRs for moderate/severe exacerbations as RRs for severe exacerbations (mepolizumab + SoC versus dupilumab + SoC) would not materially change the results. An additional scenario is presented in Table 4 which tested this assumption. Assuming the composite RRs for severe exacerbations (i.e., the same values used for moderate/severe exacerbations), results in only modest effects on the cost-effectiveness outcomes. When assuming RR = 1, mepolizumab becomes a less costly and less effective intervention compared with dupilumab, with modest impact on the net health benefit (NHB). It should be noted that assuming RR = 1 is a conservative approach.

Table 4: EAG's additional scenario results (mepolizumab + SoC versus dupilumab + SoC)

Scenario	Incremental costs	Incremental QALYs	ICER (mepolizumab versus dupilumab)	Incremental NHB (mepolizumab versus dupilumab) @ £30k
Company base-case	██████	████	Dominant	2.39
Composite RRs for severe exacerbation	██████	████	Dominant	2.30
RR=1 for severe exacerbations	██████	██████	Less costly, less effective (SW quadrant of CE plot)	2.27
Source: Modified from Table 4.33 in EAG report ³ Abbreviations: CE = cost effectiveness; ICER = incremental cost-effectiveness ratio; NHB = net health benefits; QALY = quality-adjusted life years; RR= rate ratio; SW = south west.				

In summary, the EAG considers the use of composite RRs for moderate/severe exacerbation to be appropriate. Sensitivity analyses show that using combined RRs produces only minimal changes in cost-effectiveness results, and thus the chosen approach does not raise any material concerns.

References

- 1 GSK. *Mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237] Company evidence submission (Appendix B) [CON]*. London, UK: GlaxoSmithKline; 2025.
- 2 NICE. *Dupilumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID6235]*. London, UK: National Institute for Health and Care Excellence; 2025. Available from: <https://www.nice.org.uk/guidance/indevelopment/gid-ta11246> [Accessed 24-11-25].
- 3 Tanner L, Bhattarai N, Garcia Gonzalez-Moral S, Jayachandran L, Wallace SA, Lanyi K, Whitehall J, Williams O, Kenny RRW, Ashgharzadeh A, Sagoo GS, Norman G, Thomson KH. *Mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237]: A single technology appraisal. External Assessment Group (EAG) Report*. Newcastle University: Newcastle TAR Group; 2026.

Single Technology Appraisal

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

EAG Addendum – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, [NICE health technology evaluations: the manual](#)).

You are asked to check the EAG addendum to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 23 March** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as **confidential** should be highlighted in turquoise and all information submitted as **depersonalised data** in pink.

Issue 1 Error in reporting

Description of problem	Description of proposed amendment	Justification for EAG comment amendment	EAG response
Factual accuracy of statement “particularly with the comparison with dupilumab given that a much higher rate of severe exacerbations occurred at baseline during the mepolizumab trials (██████████) compared to the dupilumab trials (n = 242, 25.8%) (see Table 34 in the CS).”	We suggest that this statement is removed.	The baseline number of severe exacerbations referenced by the EAG for the restricted mepolizumab populations are incorrectly reported in Table 34 in the CS. This is a reporting error by the company. The percentage of patients with 0 severe exacerbations at baseline reported in Table 34 in the CS for the restricted mepolizumab populations instead corresponds to patients with ≥1 severe exacerbations at baseline. Similarly, the percentage of patients with ≥1 severe exacerbations at baseline reported in Table 34 in the CS for the restricted mepolizumab populations corresponds to patients with 0 severe exacerbations at baseline.	Since the data was incorrectly reported in the CS, we are happy to remove this sentence along with the subsequent sentence which offered an explanation for the (erroneous) higher rate of severe exacerbations in the mepolizumab compared to the dupilumab trials at baseline, as follows: “<i>A possible explanation for this discrepancy could be due to the dupilumab trials being undertaken during the COVID pandemic, where people were commonly having less severe exacerbations.</i>”

		The percentages reported for the combined BOREAS/NOTUS trials in Table 34 in the CS are accurate. We have checked the figures in Section 2.10 of the CS and can confirm that, aside from one minor decimal-place adjustment in Table 33 and two minor decimal-place adjustments in Table 34, there are no other reporting errors. We have uploaded a corrected version of these tables.	

Single Technology Appraisal

Mepolizumab for reducing eosinophilic exacerbations of chronic obstructive pulmonary disease [ID1237]

EAG report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, [NICE health technology evaluations: the manual](#)).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Thursday 29 January** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as **confidential** should be highlighted in turquoise and all information submitted as **depersonalised data** in pink.

Issue 1 Ambiguous text or typographical errors affecting interpretation

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 2.1.1, page 29 “Citing unpublished research, ²¹ the Company describes caregiving in COPD as imposing a substantial emotional, physical, social, and financial burden, particularly during exacerbations.”	Update text to: “Citing ~~unpublished~~ research ~~from COPD voices~~ , [update reference] the Company describes caregiving in COPD as imposing a substantial emotional, physical, social, and financial burden, particularly during exacerbations.”	COPD voices has been published kcl.ac.uk/sims/assets/copd-voices-final-29042025.pdf	Thank you for this clarification – the changes have been made in line with this recommendation.
Section 2.2, Table 2:2, page 32 Under “Treatment guidelines” “The Company cite the NICE NG1151 COPD guidelines and the international GOLD 2025 report; ²⁹ The GOLD report has recently undergone a major revision: the GOLD 2026 report. ²⁹ ”	Update text to: “The Company cite the NICE NG1151 COPD guidelines and the international GOLD 2025 report (~~which was the most recent version at the time of the Company’s submission~~); ²⁹ The GOLD report has recently undergone a major revision: the GOLD 2026 report. ²⁹ ”	The proposed textual clarification ensures there is no ambiguity regarding the inclusion of the most up-to-date guidelines available at the time of the Company’s submission.	Thank you for this clarification – we have made the suggested changes.
Section 2.2.1, page 34 “The EAG note that the GOLD 2025 report has now been	Update text to: “The EAG note that, ~~subsequent to the Company submission~~ , the		

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
revised as a major revision and the GOLD 2026 report is now available. ²⁹	GOLD 2025 report has undergone major revisions, and the GOLD 2026 report is now available. ²⁹		
Section 2.2.3, page 37 “(defined as ≥ 2 moderate or ≥ 1 severe exacerbations within 12 months) of an eosinophilic phenotype (defined as ≥ 300 cells/μL) on a combination of an ICS, a LABA, and a LAMA (CS Section 1.4.6).⁶”	Update text to: “(defined as ≥ 2 moderate or ≥ 1 severe exacerbations within 12 months) of an eosinophilic phenotype (defined as BEC ≥ 300 cells/μL) on a combination of an ICS, a LABA, and a LAMA (CS Section 1.4.6).⁶”	The proposed amendment clarifies the biomarker used to define the eosinophilic phenotype.	Thank you for this clarification – we have made the suggested changes.
Section 4.2.3, page 153 “...Company’s base-case were adults with uncontrolled COPD of an eosinophilic phenotype (defined as ≥ 300 cells/μL)...”	Update text to: “...Company’s base-case were adults with uncontrolled COPD of an eosinophilic phenotype (defined as BEC ≥ 300 cells/μL)...”		
Section 3.3, Table 3:8, pages 87–90 All instances using “mITT-300 population” when referring to the	Please update “mITT-300 population” to “mITT-300 subgroup” when referring to the individual trial subgroups for all instances in this table.	The proposed amendment aims to avoid any confusion when referring to the pooled mITT-300 population (comprising MATINEE mITT	Thank you for your suggestions, we have implemented in each case.

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
individual METREX trial subgroup		plus the BEC ≥ 300 cells/ μ L at screening subgroups from METREX and METREO) versus the individual mITT-300 subgroups from the METREX, and METREO trials.	
Section 3.3, Table 3:9, pages 90–93	Please clarify that data reported are from the mITT-300 subgroup in each row of this table, except for adverse events where it should be clarified that these are reported in the safety population (because safety does not vary by eosinophil level).		
Section 3.3.1, page 96 “In the METREO trial, the proportion of females was higher in the 100 mg mepolizumab arm compared to the placebo arm (40% vs 32%), while the proportion of males was lower (60% vs 68%).”	Update text to: “In the mITT-300 subgroup of the METREO trial, the 100 mg mepolizumab arm included a higher proportion of females than placebo (40% vs 32%) and a lower proportion of males (60% vs 68%).”		
Section 3.3.1 page 96–97 “In the METREX trial, there was a higher proportion of patients	Update text to: “In the mITT-300 subgroup of the METREX trial, there was a		

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
with mMRC ≥ 2 , indicating more severe dyspnoea (breathlessness), in the 100mg mepolizumab arm compared to the placebo arm.”	higher proportion of patients with mMRC ≥ 2 , indicating more severe dyspnoea (breathlessness), in the 100mg mepolizumab arm compared to the placebo arm.”		
Section 3.3.2, page 99 “However, in the METREO trial, for the mITT-300 analysis group...”	Update text to: “However, in the METREO trial, for the mITT-300 analysis subgroup... ”		
Section 3.5.3, page 132 “The MAIC included ■ of ■ patients from the mepolizumab arm and ■ of ■ patients arms of the MATINEE trial.”	Update text to: “The MAIC included ■ of ■ patients from the mepolizumab arm and ■ of ■ patients from the placebo arms of the MATINEE trial.”	Correcting typographical error.	Thanks for your comment. This has now been corrected.
Section 3.7.2, page 137 “However, statistical power for the primary endpoint was achieved for the mITT-300 population in MATINEE trial.”	Update text to: “ Analyses of the primary endpoint (and additional analyses) appear to have been underpowered in METREX and METREO, where the mITT-300 population was analysed as a	The proposed amendment better reflects the BEC threshold in the MATINEE trial.	Thanks for your comment. This has now been updated as requested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
	subgroup. In contrast, MATINEE defined the mITT population using a blood eosinophil count (BEC) threshold applied to all participants, and statistical power for the primary endpoint was achieved for the mITT-300 population in this trial.”		
Section 4.2.3, page 154 “The expert noted that, in clinical practice, a patient does not need to present with a BSE threshold ≥ 300 cells/ μ L to be considered as having uncontrolled COPD”	Update text to: “The expert noted that, in clinical practice, a patient does not need to present with a BEC threshold ≥ 300 cells/ μ L to be considered as having uncontrolled COPD”	Typographical error.	Thanks for your comment. This has now been updated as requested.

Issue 2

Errors or inconsistent reporting of clinical trial data

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 2.3.1, page 48 “...whereas the Company defines the population of interest in the CS as adult	Update text to: “...whereas the Company defines the population of interest in the CS as adult patients with uncontrolled COPD (defined	Incorrect terminology.	Thank you for highlighting - this has now been amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
patients with uncontrolled COPD (defined as ≥ 2 moderate or ≥ 1 severe uncontrolled exacerbations within 12 months) of an eosinophilic phenotype (BEC ≥ 300 cells/ μ L) on a combination of an ICS, a LABA, and a LAMA.”	as ≥ 2 moderate or ≥ 1 severe ~~uncontrolled~~ exacerbations within 12 months) of an eosinophilic phenotype (BEC ≥ 300 cells/ μ L) on a combination of an ICS, a LABA, and a LAMA.”		(as has the text in the decision problem).
Section 2.3.1, page 49 “It is unclear exactly which definitions of exacerbation severity were used in the clinical trials”	Please can the EAG provide further clarification in the text on what is meant by this statement or remove the statement.	As stated in the inclusion criteria of the clinical trials, a moderate exacerbation was defined as use of systemic corticosteroids (IM, IV or oral) and/or treatment with antibiotics. A severe exacerbation was defined as requiring hospitalisation.	This text has now been amended: <i>Eligibility for the trial reflected NICE [NG115] recommendations for triple therapy (LAMA + LABA + ICS),¹ including patients with a history of frequent (≥ 2 moderate) and/or severe (≥ 1) exacerbations in the preceding year.</i>
Section 3.2, Table 3:4, page 69 Under “Eligibility criteria” “METREO included adult patients, ≥ 40 years with clinically	The EAG report inconsistently highlights exclusion criterion across the METREX, and METREO trials. It flags the exclusion of patients with certain lung, cardiac, and other unstable diseases in METREO;	Consistent reporting of eligibility criteria across trials and clarification of the	We have updated the eligibility criteria, which are now consistent, except for METREO we have

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
documented COPD for at least 1 year, history of exacerbations within the last year, history of exacerbations while on triple therapy (ICS + LAMA + LABA), and taking triple therapy for at least 3 months prior to screening. Participants with certain lung, cardiac, and other unstable diseases were excluded from METREO.” Section 3.2, Table 3:5, page 72 “METREX included adults ≥40 years with moderate-to-very severe COPD (GOLD 2–4), ≥2 moderate exacerbations (systemic corticosteroids and/or antibiotics) or ≥1 severe exacerbation (hospitalisation) in prior 12 months who were stable ICS-based triple therapy for ≥3 months. No eosinophil thresholds were required for enrolment.”	however, METREX applied the same exclusion criteria. The report also states that no eosinophil thresholds were required for enrolment in METREX, which was also the case for METREO. Please ensure the criteria are described consistently for both trials.	trial populations versus the NICE scope.	specified that patients were required to have ‘<i>type 2 inflammation (BEC ≥150 cells/μL at screening or ≥300 cells/μL in prior 12 months)</i>’, whereas in METREX we have stated that ‘<i>no eosinophil threshold was required for enrolment</i>’. This wording is taken from table 5 in the company submission (Section 2.2, Table 5, Population domain).²

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 3.2.1, page 78 “Differences between trials include study locations, as MATINEE recruited 23 participants (3%) in UK sites and METREO included eight (4%) while METREX did not include UK sites.”	Update text to: “Differences between trials include study locations, as MATINEE recruited 23 participants (3%) in UK sites and METREO recruited 22 participants (3%), while METREX did not include UK sites.”	The value reported for MATINEE reflects the total number of UK patients across the mepolizumab and placebo arms. In contrast, reporting for METREO is inconsistent, providing the number of UK patients in the mepolizumab 100 mg arm only. The proposed amendment aligns reporting by updating METREO to present the total number of UK patients across the mepolizumab 100 mg, 300 mg, and placebo arms.	The text has been amended as per the company comment
Section 3.2.1, page 78–79 “...with MATINEE using the most stringent criteria ($\geq 300/\mu\text{L}$ at screening or ≥ 150 cells/μL in the prior 12 months)”	Update text to: “with MATINEE using the most stringent criteria ($\geq 300/\mu\text{L}$ at screening and ≥ 150 cells/μL in the prior 12 months)”	Aligned with MATINEE including criteria.	Thank you. We have corrected this error.

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 3.3, Table 3:7, page 83 Under “Drop-out rate” “[REDACTED] ...”	Update text to: “[REDACTED] ...”	Typographical error may affect interpretation.	Thank you for pointing this out. We have now corrected this error.
Section 3.3, Table 3.7, page 85" Under “Adverse effects of treatment” “The only notable differences were a higher number of patients experiencing heart failure events in the mepolizumab group (6/403 vs. 3/401 with placebo), and a higher number of other cardiovascular events in the placebo group (6/401 vs. 2/403 with mepolizumab).”	Update text to: “The only notable differences were a higher number of patients experiencing CV death in the mepolizumab group (6/403 vs. 3/401 with placebo), and a higher number of non-fatal MI in the placebo group (6/401 vs. 2/403 with mepolizumab).”	The proposed amendment matches the outcome wording by the CSR for these data points.	The text has been amended as per the company comment.
Section 3.3, Table 3:9, page 91 Under “Dropout rate” “The overall study withdrawal rate for METREO was [REDACTED] which is considered acceptably low. There was differential dropout	If keeping this text, the dropout values need to be marked up as shown in the left-hand column, as they are unpublished data from the CSR. In addition, it needs to be clarified that these dropout data are for the METREO	The proposed amendment provides clarity on the analysis population being described and is better aligned with the reporting	The EAG has updated to text in the dropout rate section of Table 3.9 to better align with the reporting in the

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
rate between the treatment arms, the lowest drop out was in the 100mg mepolizumab arm [REDACTED] compared to with a dropout rate of [REDACTED]% in the placebo arm and [REDACTED] in the 300mg mepolizumab arm. The primary reason for study withdrawal was AEs (including deaths) across all arms”	mITT population, not the mITT-300 subgroup. However, we propose aligning this information with the critique of METREX in Table 3.8 of the EAG report, which reports dropout rates for the METREX mITT-300 population. Therefore, we suggest replacing the text with: “There was a [REDACTED] [REDACTED] [REDACTED] The primary reason for study withdrawal was [REDACTED] [REDACTED] [REDACTED] [REDACTED]	of the METREX trial in Table 3.8.	METREX trial using the proposed wording suggested by the company and ensuring that data used from the CSR has been highlighted as confidential.

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
	The cross reference will also need to be updated to the Pooled analysis CSR Tables 16 and 17.		
Section 3.3, Table 3:9, page 91 Under “Primary efficacy outcome” “In METREO the annualised rate of moderate or severe exacerbations was [REDACTED].”	Update text to: “In the METREO mITT-300 subgroup, the annualised rate of moderate or severe exacerbations was [REDACTED].”	The proposed amendment clarifies the data are for the mITT-300 subgroup and corrects an error in the reported data point.	The EAG has amended the text as proposed to clarify the mITT subgroup.
Section 3.3.2, page 99–100 “However, in the METREO trial, for the mITT-300 analysis group, there was variation in withdrawal rates between those receiving 100mg mepolizumab ([REDACTED]% withdrawal) versus placebo ([REDACTED]% withdrawal). Similarly, treatment discontinuation was lower in patients who received mepolizumab 100mg, with [REDACTED]%	Update text, including the CON marking to: “However, in the METREO trial, for the mITT-300 analysis group, there was variation in withdrawal rates between those receiving 100mg mepolizumab ([REDACTED]% withdrawal) versus placebo ([REDACTED]% withdrawal). Similarly, treatment discontinuation was lower in patients who received mepolizumab 100mg, with [REDACTED]% of patients in this group prematurely discontinuing treatment ([REDACTED]%	The proposed amendment corrects errors in reported data points and also uses the correct CON marking.	Thank you for highlighting, the EAG has amended the data points and updated the CON marking.

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
of patients in this group prematurely discontinuing treatment (■■■% withdrawing from the study at the same time) compared to ■■■% in the placebo group prematurely discontinuing treatment (■■■% withdrawing from the study at the same time)."	withdrawing from the study at the same time) compared to ■■■% in the placebo group prematurely discontinuing treatment (■■■% withdrawing from the study at the same time)."		

Section 3.3.7, page 103–104 “The prespecified and post-hoc analyses shown below in Figure 3.1, presents results of showing that 13 of the 40 subgroup analyses achieved statistical significance in favour of mepolizumab (namely 104 weeks treatment duration, people aged ≥65 years, males, White, medium BMI, ≤2 exacerbations in previous year, no severe exacerbation in previous year, both with or without CB at baseline, ≥2 mMRC scores, severe airflow obstruction and in people with CV comorbidity).”	Update text to: “The prespecified and post-hoc analyses shown below in Figure 3.1, presents results of showing that 13 of the 40 subgroup analyses achieved statistical significance in favour of mepolizumab (namely 104 weeks treatment duration, people aged ≥65 years, males, White, medium BMI, ≤2 exacerbations in previous year, no severe exacerbation in previous year, both with or without CB at baseline, ≥2 mMRC scores, severe airflow obstruction and in people with CV comorbidity, Investigator assessed CB, and people who received corticosteroids).”	The proposed amendment includes the missing subgroups.	We thank the company for their comment. We have updated the text as follows: <i>The prespecified and post-hoc analyses shown below in Error! Reference source not found., presents results of showing that 14 of the 40 subgroup analyses achieved statistical significance in favour of mepolizumab (namely 104 weeks treatment duration, people aged ≥65 years, males, White, medium BMI, ≤2 moderate/ severe COPD exacerbations in previous year, no severe COPD exacerbations in</i>

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
			<i>previous year, presence and absence of CB at baseline, ≥ 2 mMRC scores, severe airflow obstruction and in people with CV comorbidity, investigator assessed CB, and people who received corticosteroids).</i>” Please note that we have changed the number of sub-groups with a significant effect from 13 to 14 as presence and absence of CB at baseline represents two subgroups rather than one.
Section 3.5.3, page 133	Update text to:	The 95% CrI is narrower for Population 2 than	The text has now been updated as per

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
“The EAG notes that the 95% Crls for the ML-NMR result is narrower for population 1 than for population 2, which is likely to reflect the increased sample size in the latter.”	“The EAG notes that the 95% Crls for the ML-NMR result is narrower for population 2 than for population 1, which is likely to reflect the ~~increased~~ larger effective sample size following matching in ~~the latter~~ Population 2.”	Population 1. The direction of the comparison has been corrected to align with the underlying sample sizes. Population 1 includes 334 patients based on CB per investigator assessment, reducing to 181 after matching, whereas Population 2 includes 518 patients based on CB per SGRQ-C, reducing to 309 after ESS matching. The narrower 95% Crls observed for population 2 are therefore consistent with its larger matched sample size.	the company comment.

Issue 3 Errors in reporting of the SLR

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 3.1.2, page 57	Update text to:	The proposed amendment clarifies the fields applied in	Thank you for highlighting this – we

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
“The use of the DC (date created) and DD (first date) field in the updates of the Embase and Medline search, created some minor concerns. It is important to assess whether this field is the most appropriate choice compared to alternatives (e.g., year of publication), as the behaviour of DC or DD is dependent on current indexing practices. If applied inappropriately, this could lead to either increased noise or the exclusion of relevant records.”	“The use of the DC (date created) and DD (first date) fields in the updates of the Embase and ED (entry date) and DT (create date) in MEDLINE search created some minor concerns. It is important to assess whether this field is the most appropriate choice compared to alternatives (e.g., year of publication), as the behaviour of DC or DD is dependent on current indexing practices. If applied inappropriately, this could lead to either increased noise or the exclusion of relevant records.”	each database. DC and DD were used in the Embase update search, while ED and DT were used in MEDLINE.	have made the suggested change.

Issue 4 Description of modelling approaches

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 1.6, Table 1:1, page 25 Under “Company’s base-case assumption” heading	Update text to: “2 nd year discontinuation rate from MATINEE trial for mepolizumab	The company’s base case assumption is to use the MATINEE 2 nd year discontinuation rate for year 2	The EAG accepts the company’s suggestion, that the description of the company base-case

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
“Lower bound (15%) of annual discontinuation (range of estimates from the real world between 15% to 25.8%) for mepolizumab and dupilumab for Year 2 onwards in the model”	and dupilumab for Year 2 onwards in the model” Please ensure that if the 2nd year MATINEE discontinuation rate is also reported in an amendment, that it is marked confidential.	onwards in the model. 15% annual discontinuation from the dupilumab NICE company submission was used in a scenario analysis.	assumption needs to be updated for better clarity. We have updated the text as: <i>“The annualised discontinuation rate observed over the second year of the MATINEE trial (■) was scaled to a per cycle probability of discontinuation (■ %) and was used in the model for mepolizumab and dupilumab from Year 2 onwards. Alternatively, Lower bound (15%) of annual discontinuation (range of estimates from the real world between 15% to 25.8%) from the NICE dupilumab submission was explored as a scenario for mepolizumab and</i>

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
			<i>dupilumab for Year 2 onwards in the model.</i> The corresponding text in Section 4.4.2, Table 4:31 was also updated in the report.

Issue 5 Errors in reporting of economic model results

Description of problem	Description of proposed amendment	Justification for amendment	EAG Comment
Section 4.3.2.1, page 190 “The NHB of mepolizumab + SoC compared with dupilumab + SoC and SoC alone were 0.07 and 3.49 respectively, at a £20,000 per QALY threshold”	Update text to: “The NHB of mepolizumab + SoC compared with SoC alone and dupilumab + SoC were 0.07 and 3.49 respectively, at a £20,000 per QALY threshold”	The proposed amendment correctly orders the comparisons and respective NHB's.	The EAG thank the company for their comment – we have made the suggested changes.
Section 4.3.2.1, page 190 “Table 4:23 presents the net health benefit (NHB) and net monetary benefit (NMB) results from the probabilistic analysis”	Update text to: “Table 4:23 presents the incremental net health benefit (NHB) and incremental net monetary benefit (NMB) results from the probabilistic analysis”	The proposed amendment ensures consistency between the reporting of NHB, which is incremental, and the reporting of NMB. It also ensures alignment with the table headings.	The EAG thank the company for their comment – we amended the text and updated the suggested changes in values for incremental NMB for mepolizumab + SoC versus

Description of problem	Description of proposed amendment	Justification for amendment	EAG Comment
“The NMB for mepolizumab + SoC was £115,209 at the £20,000 threshold, which was the highest among the treatments evaluated” Section 4.3.2.1, Table 4:23, page 191 The EAG have reported the NMB at thresholds of £20k and £30k per QALY, for each comparison.	Update text to: “The incremental NMB for mepolizumab + SoC vs SoC was £1,463 at the £20,000 threshold” Update table to include incremental NMB as mentioned in table heading “(mepolizumab versus comp)”. Values versus SoC are £1,463 and £10,508 at the £20k and £30k per QALY thresholds, respectively. Values versus dupilumab + SoC are £53,126 and £56,229 at the £20k and £30k per QALY thresholds, respectively.		SoC alone. But the incremental NMB for mepolizumab + SoC versus dupilumab + SoC was £69,755 and £72,858 at 20K and 30K respectively. These values were updated in Table 4:23.
Section 4.3.2.3, Table 4:26, page 199 The EAG report an ICER of £18,494 for mepolizumab + SoC versus SoC, scenario 12.	Update scenario number to 11.	Scenario 12 impacts the discontinuation rate for dupilumab + SoC in Year 2 onwards, whilst assuming the base-case discontinuation rate for mepolizumab + SoC.	The EAG thank the company for their comment – we have made the suggested changes.

Description of problem	Description of proposed amendment	Justification for amendment	EAG Comment
		The ICER result reported corresponds to scenario 11 in the table above, where the discontinuation rate for mepolizumab + SoC is set to 15%, as reported in the RWE.	
Section 4.3.2.3, Table 4:30, page 204 The EAG report an incremental cost of [REDACTED] for scenario 24 in the comparison of mepolizumab + SoC versus dupilumab + SoC.	Update incremental cost to [REDACTED]	This value has been incorrectly copied.	The EAG thank the company for their comment – we have made the suggested changes.

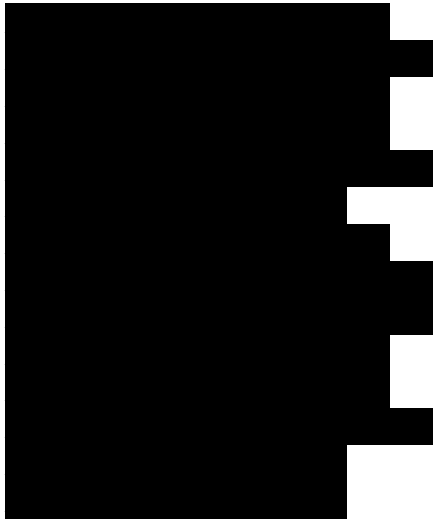
Issue 6

Incorrect marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EG comment
Section 3.2, Table 3:5, page 74, Under “Allocation concealment”	The Company do not consider these methods as CON.	Please remove the CON marking from: “The EAG considers the allocation process appropriate, as it appears to have been fully automated,	This has been amended as per the company comment.

Location of incorrect marking	Description of incorrect marking	Amended marking	EG comment
		reducing the risk of interference or prediction by trial staff.”	
Section 3.2, Table 3:5, page 74, Under “Blinding”	The Company do not consider these methods as CON.	Please remove the CON marking from: “The Company provided details of their blinding procedure, including details of which parties were blinded (investigators, subjects, and those involved in the administration of treatment and study assessments), how blinding was implemented and details of the emergency unblinding procedure”	This has been amended as per the company comment.
Section 3.2.1, page 78	This trial inclusion criterion is publicly available online (ClinicalTrials.gov).	Please remove the CON marking from: “...(using an ICS at a dose ≥ 500 mcg/day fluticasone propionate (FP) dose equivalent plus LABA plus LAMA for a minimum of 3 months prior to screening), severity...”.	This has been amended as per the company comment.

Location of incorrect marking	Description of incorrect marking	Amended marking	EG comment
Section 3.3, Table 3:7, page 84 Under “Frequency of moderate or severe exacerbations”	The Company do not consider these data CON and these data are unmarked in the Company submission.	Please remove the CON marking from: “At Week 104, mepolizumab demonstrated a statistically significant 21% reduction in the annualised rate of moderate/severe exacerbations compared with placebo in the mITT population (RR 0.79; 95% CI 0.66–0.94; p=0.011).”	Thank you for pointing this out. We have now removed the CON marking on this sentence.
Section 3.3, Table 3:7, page 84–85 Under “Symptom control (E-RS:COPD Score)”	These data are unpublished. GSK currently has no plans to publish these results. In case this should change, GSK will inform NICE accordingly.	Please mark up as follows: “minimal and non-significant differences in mean change from baseline [REDACTED] vs. [REDACTED]; mean difference [REDACTED]). A [REDACTED] proportion of participants in the mepolizumab group experienced no improvement or worsening symptoms ([REDACTED]).”	Thank you for pointing this out. We have now included the CON marking on these data.
Section 3.3, Table 3:9, page 91 Under “Key secondary efficacy outcomes’ Time to	These data are marked up in the Company submission, Table 23.	Please mark up as follows: “In the METREO, in the mITT-300 subgroup, the Week 52 probability (%) of an exacerbation was [REDACTED]”	The EAG has updated the text with the proposed amendments and added the CON

Location of incorrect marking	Description of incorrect marking	Amended marking	EG comment
			
Section 3.3, Table 3:10, page 96 Under “Sub-group analyses”	Subgroup analysis results for the severity of airflow limitation (GOLD reports) are not marked as CON in the Company submission, Table 31.	Please mark up as follows:  severity of airflow limitation (Severe: $\geq 30\%$-<50% predicted),  	This has been amended as per the company comment.

Location of incorrect marking	Description of incorrect marking	Amended marking	EG comment
Section 3.3.7, page 106	Pooled mITT-300 subgroup results are marked CON in the Company submission	Please mark up as follows: “Of these, [REDACTED] achieved statistical significance favouring mepolizumab over placebo.”	This amendment has been made as per the company comment.
Section 4.2.5.1, page 158	This is marked as CON in the Company submission.	Please mark up as follows: “...was used to estimate the proportional increase relative to mepolizumab ([REDACTED]), [REDACTED] [REDACTED]”	The EAG accepts the company’s proposed changes, but the confidential markings are applied to the values and not the text. The following amendment has been made based on the comment – “...mepolizumab ([REDACTED]), equivalent to ([REDACTED]) increase.”
Section 4.2.6, page 166	The second year MATINEE discontinuation rate is marked CON in the company submission.	Please mark up as follows: “...[REDACTED] % probability discontinuation per cycle from MATINEE were both applied”	This amendment has been made.

Location of incorrect marking	Description of incorrect marking	Amended marking	EG comment
Section 4.3.2.1, page 190–191	The Company do not consider these data CON and are unmarked in the Company submission.	Please remove the CON marking from: “The probability that mepolizumab + SoC is cost-effective was 70.4% and 99.7% at willingness-to-pay threshold of £20,000 and £30,000 per QALY, respectively.	This amendment has been made.
Section 4.3.2.2, Table 4:28, page 202	The second year MATINEE discontinuation rate is marked CON in the company submission.	Please mark up as follows: “■ % discontinuation per cycle beyond year 1 (applied to mepolizumab and dupilumab)”	Thank you for the comment. Table 4:28 is in fact in Section 4.3.2.3, however this proposed amendment has been made.
Section 4.3.2.2, Table 4:28, page 203	Disutilities are marked CON in the company submission.	Please mark up as follows: “The disutility of (■) was applied to Frequent severe (9-12 months) health state” “Disutility in the frequent severe (9–12 months) state is set equal to that of the frequent severe (6-9 months) state (■).”	Thank you for the comment. Table 4:28 is in fact in Section 4.3.2.3, however the proposed amendment has been made.

References

1. NICE. Chronic obstructive pulmonary disease in over 16s: diagnosis and management [NG115]. London, UK: National Institute for Health and Care Excellence; 2018. Available from: <https://www.nice.org.uk/guidance/ng115> [Accessed 24-11-25].
2. GlaxoSmithKline. Mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [ID1237] Company evidence submission [CON]. London, UK: GlaxoSmithKline; 2025.