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Mepolizumab for treating severe eosinophilic asthma: An Evidence Review Group perspective of a NICE Single Technology Appraisal

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Short title: Mepolizumab for treating severe eosinophilic asthma: An ERG perspective of a NICE STA

Abstract

As part of its single technology appraisal (STA) process, the National Institute for Health and Care Excellence (NICE) invited the company (GlaxoSmithKline) that manufactures mepolizumab (Nucala®) to submit evidence on the clinical and cost-effectiveness of mepolizumab for the treatment of severe eosinophilic asthma. The School of Health and Related Research Technology Appraisal Group (ScHARR-TAG) at the University of Sheffield was commissioned to act as the independent Evidence Review Group (ERG). The ERG produced a review of the evidence for the clinical and cost-effectiveness of mepolizumab as add-on to standard of care (SoC) compared with SoC and omalizumab, based upon the company's submission to NICE. The clinical effectiveness evidence in the company's submission is based predominantly on three randomised controlled trials (DREAM, MENSA and SIRIUS) comparing add-on mepolizumab with placebo plus standard of care (SoC). The relevant population was defined in terms of degree of asthma severity (4 or more exacerbations in the previous year and/or dependency on maintenance oral corticosteroids (mOCS)) and degree of eosinophilia (a blood eosinophil count of ≥300 cells/μl in the previous year) based on *post hoc* subgroup analyses of the pivotal trials. Other subpopulations were considered throughout the appraisal, defined by different eosinophil measurements, number of exacerbations and dependency (or lack thereof) on mOCS. Statistically significant reductions in clinically significant exacerbations were observed in patients on mepolizumab compared with SoC meta-analysed across MENSA and DREAM, in the modified ITT population (rate ratio [RR]=0.51, 95% confidence interval [CI] 0.42, 0.62), as well as in the relevant population (RR=0.47, 95% CI 0.36, 0.62). In terms of quality of life, differences on the St. George's Respiratory Questionnaire in MENSA for add-on mepolizumab 100mg SC vs. placebo were 7 units and

7.5 units in the modified ITT and relevant populations respectively. There were a number of issues in the clinical evidence base which warrant caution in its interpretation. The ERG noted that the definition of SoC used in the trials differed from clinical practice, where severe patients whose asthma is uncontrolled start a treatment with mOCS. The company's economic post-consultation analysis incorporating a confidential Patient Access Scheme (PAS) estimated that the incremental cost-effectiveness ratio (ICER) for add-on mepolizumab compared with SoC was £27,418 per quality adjusted life year (QALY) gained in the relevant population if patients stopped mepolizumab after one year unless (i) the number of exacerbations decreased at least 50% or (ii) a reduction in corticosteroids dose was achieved whilst maintaining asthma control. The ERG applied an age-adjustment to all utilities and corrected the post-continuation assessment utilities, which resulted in an ICER for add-on mepolizumab compared with SoC of £29,163 per QALY gained. The ERG noted that this ICER was not robust for patients who continued treatment due to a corticosteroid dose reduction where exacerbations had decreased by less than 50%, because corticosteroids dose reduction was not allowed in the main trial in which the evidence was gathered (MENSA). The NICE Appraisal Committee (AC) concluded that add-on mepolizumab could be recommended as an option for treating severe refractory eosinophilic asthma in adults for the relevant population when the stopping rule suggested by the company was applied. The AC also concluded that the comparison between mepolizumab and omalizumab was not clinically relevant or methodologically robust.

Key points for decision makers

- Add-on mepolizumab resulted in clinically and statistically significant reductions in asthma-related exacerbation rates and an improvement in health-related quality of life.

- The cost-effectiveness of mepolizumab compared to maintenance oral corticosteroids (mOCS) or in patients on mOCS is uncertain due to the difficulties with capturing the disutilities and costs associated with long-term mOCS use.

- The appraisal committee concluded that the comparison between omalizumab and mepolizumab was not clinically relevant, since the two drugs were associated with different pathways and different populations.

- NICE recommended mepolizumab as an option for treating severe refractory eosinophilic asthma in adults with a blood eosinophil count of ≥300 cells/µl in the previous year as well as 4 or more exacerbations in the previous year and/or dependency on mOCS, if the company provided the drug with the discount agreed in the Patient Access Scheme. At 12 months, treatment should be continued only if the number of exacerbations is reduced by at least 50% or a clinically significant reduction in mOCS use is achieved while maintaining or improving asthma control.

1. Introduction

The National Institute for Health and Care Excellence (NICE) is an independent organisation responsible for providing national guidance on promoting good health and preventing and treating ill health in priority areas with significant impact. Health technologies must be shown to be clinically effective and to represent a cost-effective use of National Health Service (NHS) resources in order for NICE to recommend their use within the NHS in England. The NICE Single Technology Appraisal (STA) process usually covers new single health technologies within a single indication, soon after the UK market authorisation [1]. Within the STA process, the company provides NICE with a written submission, alongside a mathematical model that summarises the company's estimates of the clinical and cost effectiveness of the technology. This submission is reviewed by an external organisation independent of NICE, the Evidence Review Group (ERG), which consults with clinical specialists and produces a report. After consideration of the company's submission, the ERG report and a testimony from experts and other stakeholders, the NICE Appraisal Committee (AC) formulates preliminary guidance, the Appraisal Consultation Document (ACD), which indicates the initial decision of the AC regarding the recommendation (or not) of the technology. Stakeholders are then invited to comment on the submitted evidence and the ACD, after which a further ACD may be produced or a Final Appraisal Determination (FAD) is issued, which is open to appeal. An ACD is not produced when the technology is recommended within its full marketing authorisation, in which case, a FAD is produced directly.

This paper presents a summary of the ERG report [2] for the STA of mepolizumab for treating severe eosinophilic asthma and a summary of the subsequent development of the NICE guidance for the use of this drug in England. Full details of all relevant appraisal documents (including the appraisal scope, ERG report, company and consultee submissions, FAD and comments from consultees) can be found on the NICE website.[3]

2. The Decision Problem

2.1 Population (severe eosinophilic asthma)

Asthma is a broad condition characterised by inflammation of the airways leading to reversible (and in some cases, irreversible[4]) airway obstruction. Asthma symptoms include wheezing, chest tightness, cough and shortness of breath, and exacerbations (worsening) of symptoms can lead to hospitalisations and death. It is estimated that approximately 5.4 million people in England and Wales currently receive treatment for asthma.[3] Asthma varies in its severity, but in most cases can be controlled with a combination of medications, which in the UK are administered in a step-wise manner (steps 1 to 5, with 1 being the lowest step) until control is reached, according to the British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN) guidelines.[5] The level of treatment required is also a measure of the severity of the condition.

The American Thoracic Society (ATS)/European Respiratory Society (ERS) Task Force defines severe asthma as *''asthma that requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller and/or systemic corticosteroids to prevent it from becoming 'uncontrolled' or that remains 'uncontrolled' despite this therapy."*[6] These patients suffer from frequent exacerbations, despite controller medications, and have a decreased quality of life due to uncontrolled symptoms and treatment side effects, as many take oral corticosteroids long-term. The impact of exacerbations on patients varies, with some just requiring systemic corticosteroids and others a hospital stay; ultimately, some patients die from an asthma exacerbation. There were 1,242 asthma-related deaths in the UK in 2012. Severe asthmatics were found to account for 39% of deaths from asthma, [7] and the company (GlaxoSmithKline, GSK) argues that as severe asthmatics are only a small proportion of the total asthma population (5-10%), mortality is still *"an issue"* for this population.

Eosinophilic asthma is a distinct phenotype of asthma characterised by tissue and sputum eosinophilia (high levels of a type of white blood cell called eosinophils), a thickening of the basement membrane and, often, responsiveness to corticosteroids.[8] It can be present in mild, moderate or severe asthma.[8] It is, however, associated with more severe disease, late onset, atopy and steroid refractoriness. The diagnosis of eosinophilic asthma is problematic in clinical practice. Induced sputum eosinophil levels of 2%[8] are commonly interpreted as indicating eosinophilic disease, however, this test is impracticable in routine care. Alternatives include peripheral blood eosinophil counts, fractional exhaled nitric oxide (FeNO), serum immunoglobulin E (IgE), and periostin levels. However, a recent US review[8] reported that these have limited diagnostic accuracy: levels of blood eosinophils >300 cells/μL had a positive predictive value of only 50% in identifying an eosinophilic asthma phenotype (defined as sputum eosinophils of >2%); serum IgE had no correlation with eosinophilia;[9] studies relating to FeNO appeared inconsistent;[10-12] and the diagnostic utility of periostin was promising but is as yet undetermined.

Despite only moderate diagnostic accuracy being reported for blood eosinophils in the literature, the test is used in clinical practice to monitor disease.[5] There is no national or international consensus on how to interpret such tests; however, clinical advisors to the ERG stated that a level of ≥300 cells/μL in the previous 12 months is a commonly used cut-off.

2.2 Intervention

Mepolizumab (Nucala®, GSK) is a humanised anti-interleukin 5 monoclonal antibody (IgG1, kappa). Mepolizumab is indicated as an add-on treatment to standard of care (SoC) for severe refractory eosinophilic asthma in adult patients.[13] The licensed dose is 100mg administered subcutaneously (SC) every 4 weeks with the company assuming that this will be undertaken by a specialist asthma nurse. The summary of product characteristics states that the need for continued therapy should be considered at least on an annual basis as determined by physician assessment of the patient's disease severity and level of control of exacerbations. A confidential Patient Access Scheme (PAS) representing a simple discount on list price is in place for mepolizumab.

2.3 Comparators

NICE issued a final scope to appraise the clinical and cost effectiveness of mepolizumab, within its licensed indication, for the treatment of severe eosinophilic asthma. The main comparator was SoC, which, for severe asthma patients, includes the use of high-dose ICS and other controllers, such as long-acting β-agonists, leukotriene antagonists or theophyllines, and finally daily oral corticosteroids (OCS) at the lowest possible dose to achieve adequate control. For people with severe persistent allergic IgE-mediated eosinophilic asthma, the intervention was also compared with omalizumab (brand name Xolair®), a drug recommended by NICE for patients with severe IgE-mediated asthma who "need continuous or frequent treatment with oral corticosteroids". The marketing authorisation of omalizumab states that 16 weeks after the start of treatment, physicians should assess the effectiveness of the treatment, and should continue the treatment only in patients whose asthma has markedly improved. A confidential PAS is also in place for omalizumab.

3. The Independent Evidence Review Group Review

The company provided a submission to NICE on the use of mepolizumab for the treatment of patients with severe refractory eosinophilic asthma. In accordance with the process for STAs, the ERG and NICE had the opportunity to seek clarification on specific points in the company's submission, in response to which the company provided additional information. The ERG also modified the company's decision analytic model to produce an ERG base case and to assess the impact of alternative parameter values and assumptions on the model results. The evidence presented in the company's submission and the ERG's review of that evidence is summarised here.

3.1 Clinical Evidence Provided by the Company

3.1.1 Pivotal trials

The clinical effectiveness evidence in the company's submission is based predominantly on three randomised controlled trials (RCTs) comparing mepolizumab, as add-on to SoC, with placebo plus SoC in patients with severe eosinophilic asthma. Two trials (DREAM[14] and MENSA[15]) had a primary endpoint of reduction in exacerbations, whilst one (SIRIUS[16]) enrolled patients receiving maintenance oral corticosteroids (mOCS) and had a primary endpoint of reduction in OCS use. In addition, data from two open-label extension studies (COSMOS[17] and COLUMBA[18]) enrolling patients from the three RCTs are also included. Mepolizumab was provided at various doses within the trials; the doses considered here include the licensed dose of 100mg SC and the 75mg intravenous (IV) dose which is considered to be clinically equivalent to 100mg SC.[19]

3.1.2 Key sub-populations

Effectiveness and cost-effectiveness were assessed for the following post-hoc subgroups of patients from the pivotal trials:

- **Intention-to-treat (ITT) population:** All trial patients who were randomised and received at least one dose of study medication (strictly a modified intention-to-treat population).
- **Company-proposed population:** Adult severe refractory eosinophilic asthma patients with a blood eosinophil count of ≥150 cells/µl at initiation of treatment; and ≥4 exacerbations in the previous year and/or dependency on mOCS (regardless of exacerbations in previous year).
- **Company-proposed restricted population:** Adult severe refractory eosinophilic asthma patients with a blood eosinophil count of ≥150 cells/µl at initiation of treatment; and ≥4 exacerbations in the previous year.
- **mOCS users with <4 exacerbations (denoted "stable mOCS" by the ERG):** Adult severe refractory eosinophilic asthma patients with a blood eosinophil count of ≥150 cells/µl at initiation of treatment and dependency on mOCS but <4 exacerbations in the previous year. This constitutes the patients in the company-proposed population who are not within the proposed restricted population. The term "stable" is used for ease of reading and refers to having fewer than four exacerbations in the previous year.
- **Committee-preferred population:** Adult severe refractory eosinophilic asthma patients with a blood eosinophil count of ≥300 cells/µl in the previous year; and ≥4 exacerbations in the previous year and/or dependency on mOCS (regardless of exacerbations in previous year).

The company's rationale for the proposed population was based on *post hoc* modelling and subgroup analyses of DREAM and MENSA, indicating a greater reduction in exacerbations for mepolizumab versus placebo for patients with (a) higher baseline blood eosinophils and (b) more previous

exacerbations. In addition, the company included mOCS users with a blood eosinophil level of ≥150 cells/µl in the proposed population (regardless of previous exacerbations) claiming mOCS users are likely to be a severe group and that there are clinical benefits to reducing use of mOCS. The company also provided data for the proposed restricted population. The ERG requested analyses for the stable mOCS population, as the efficacy of mepolizumab in these patients is expected to be lower than in the proposed restricted population. The AC proposed an alternative population (termed committee-preferred population), modifying the eosinophil level threshold in the company-proposed population, after concluding that a blood eosinophil level of ≥300 cells in the previous year was more clinically significant of high eosinophil levels than ≥150 cells/µl at screening.

3.1.3 Key clinical effectiveness results

Clinically significant exacerbations were defined in all three trials as worsening of asthma requiring use of systemic corticosteroids (or double the maintenance dose) and/or hospitalisation and/or emergency department (ED) visits. The rate ratios (RRs) for clinically significant exacerbations for add-on mepolizumab versus placebo observed in MENSA, DREAM and SIRIUS are shown in Table 1.

Table 1: Rate ratios† for clinically significant exacerbations for add-on mepolizumab vs. placebo (95% CI) observed in MENSA, DREAM and SIRIUS

Trial	Treatment arm	Modified ITT population	Proposed population	Proposed restricted population	Stable mOCS	Committee-preferred population
	75mg IV	0.53 (0.39, 0.71)	0.40 (0.24, 0.67)	0.39 (0.22, 0.68)	0.45 (0.16, 1.24)	0.47 (0.30, 0.73)
	100mg SC	0.47 (0.35, 0.63)	0.50 (0.32, 0.78)	0.39 (0.23, 0.67)	0.93 (0.42, 2.03)	0.56 (0.37, 0.85)
	75mg IV and 100mg SC	0.50 (0.39, 0.64)	Not reported	Not reported	Not reported	Not reported
DREAM	**75mg IV**	0.52 (0.39, 0.69)	0.36 (0.24, 0.55)	0.31 (0.18, 0.53)	0.41 (0.19, 0.86)	0.42 (0.27, 0.64)
DREAM + MENSA ‡	**75mg IV and 100mg SC**	0.51 (0.42, 0.62)	0.41 (0.31, 0.55)	0.35 (0.25, 0.50)	0.55 (0.32, 0.92)	0.47 (0.36, 0.62)
SIRIUS	**100mg SC**	0.68 (0.47, 0.99)	0.77 (0.51, 1.17)	0.81 (0.40, 1.64)	0.75 (0.44, 1.29)	0.60 (0.40, 0.90)

Abbreviations: IV: intravenous; SC:subcutaneous; ITT:intention-to-treat; mOCS: maintenance oral corticosteroids;
†Analysis of number of exacerbations performed using a negative binomial model with covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), region, and baseline % predicted FEV_1, and with logarithm of time on treatment as an offset variable.
‡Synthesised using random-effects meta-analysis

For exacerbations requiring hospitalisation, RRs for mepolizumab (100mg SC and 75mg IV groups combined) vs. placebo, meta-analysed across MENSA and DREAM, were: RR=0.50 (95% CI 0.28, 0.89) in the modified ITT population; RR=0.44 (95% CI 0.19, 1.02) in the proposed population; RR=0.43 (95% CI 0.16, 1.12) in the proposed restricted population; RR=0.53 (95% CI 0.10, 2.75) in the stable mOCS population; and RR=0.44 (95% CI 0.18, 1.05) in the committee-preferred population. In SIRIUS, hospitalisation numbers were low (ITT: 7 for placebo vs. 0 for mepolizumab). The RRs for

exacerbations requiring hospitalisation or ED visits showed a similar pattern to those of exacerbations requiring hospitalisation. In terms of quality of life, differences on the St. George's Respiratory Questionnaire (SGRQ) for MENSA and SIRIUS for mepolizumab vs. placebo ranged from 5 to 13 units ($p<0.001$ for meta-analysed results) in all sub-populations except stable mOCS (minimal clinically important difference [MCID] 4 units). Differences on the Asthma Control Questionnaire (ACQ) meta-analysed across MENSA and DREAM ranged from -0.3 to -0.8 ($p<0.001$ for all) across all sub-populations except stable mOCS (MCID 0.5 units). Differences for the Asthma Quality of Life Questionnaire (AQLQ, DREAM only) ranged from 0.1 to 0.4 (MCID 0.5 units) and were not statistically significant ($p>0.1$ for all comparisons).

3.1.4 Steroid reduction

The SIRIUS trial had a primary endpoint of percentage reduction in OCS dose whilst maintaining asthma control. Odds ratios (OR) for mepolizumab vs. placebo, analysed using a proportional odds model for the proportion achieving various categories of reduction in OCS dose whilst maintaining asthma control were: OR=2.39 (95% CI 1.25, 4.56) for ITT; OR=1.81 (95% CI 0.86, 3.79) for proposed population; OR=2.75 (95% CI 0.72, 10.59) for proposed restricted population; and OR=3.51 (95% CI 1.69, 7.25) for the committee-preferred population.

In terms of secondary outcomes in the committee-preferred population, the OCS dose was reduced by at least 50% in 57% of patients (mepolizumab) vs. 28% (placebo), resulting in an OR of 3.36 (95% CI 1.5, 7.52). A reduction in OCS dose to ≤5 mg was observed in 56% of patients (mepolizumab) vs. 28% (placebo), with an OR of 3.23 (95% CI 1.38, 7.57). In addition, OCS use was stopped completely in 16% (mepolizumab) vs. 4% (placebo), with an OR of 4.27 (95% CI 0.81, 22.49. ORs were generally statistically significant in the modified ITT population. Results were slightly more favourable (in terms of magnitude of the point estimates) in the committee-preferred population and in the proposed restricted population than the proposed population, but were not statistically significant ($p>0.05$), though patient numbers were small.

3.1.5 Subgroup analyses

The company used *post hoc* subgroup analyses to define the two proposed populations. Two options were considered for the eosinophil threshold: ≥150/μL at screening or ≥300/μL in the previous 12 months. Patients with ≥150/μL at screening had a greater reduction in exacerbations for mepolizumab versus placebo than patients with <150/μL; this was not the case when the population was subgrouped using a threshold of ≥300/μL in the previous 12 months. The company used this as the basis for focussing on patients with ≥150/μL at screening. In terms of exacerbation history, subgroup analyses in DREAM and MENSA suggested that patients with more previous exacerbations had a greater reduction in exacerbations for mepolizumab vs. placebo, though the findings were not conclusive. Potential issues relating to these sub-populations are discussed in Section 3.2.

3.1.6 Open-label extension studies

The company provided data on two open-label, non-randomised, non-controlled extension studies enrolling patients completing the pivotal RCTs. Patients in COSMOS (from MENSA and SIRIUS) either continued mepolizumab without interruption or switched from placebo to mepolizumab 100mg SC for 52 weeks. Patients in COLUMBA (from DREAM) had a ≥12--month treatment break and subsequently received mepolizumab100mg SC. COLUMBA is ongoing and patients will receive mepolizumab for up to 3.5 years. The exacerbation rate per year in COLUMBA was 0.67; this was lower than the rate of 1.24 observed in the mepolizumab arm of the modified ITT population in DREAM. The rate per year in COSMOS was 0.93; this was similar to the rate of 0.88 observed in the MENSA mepolizumab modified ITT population but was higher than the rate of 0.68 observed in the SIRIUS trial.

3.1.7 Indirect comparison of mepolizumab vs. omalizumab

The company undertook a network meta-analysis (NMA) of trials comparing mepolizumab or omalizumab to SoC. The main analysis includes the ITT populations for both mepolizumab and omalizumab. Secondary analyses used full-trial populations for omalizumab (as it was not possible to obtain data on subgroups within the omalizumab trials) but a subgroup of patients from mepolizumab trials who were also eligible for omalizumab (eosinophilic and allergic asthma). Patients in the omalizumab trials in the main analysis were less severe (≥1 exacerbation in previous year) than in the mepolizumab trials (≥2 exacerbations). The main analysis compared two double-blind mepolizumab RCTs (MENSA and DREAM) with two double-blind omalizumab RCTs (INNOVATE[20] and EXTRA[21]). Two additional open-label RCTs of omalizumab were included in secondary analyses (Niven 2008[22] and EXALT[23]).

Based on a fixed-effect NMA undertaken by the company, mepolizumab gave a statistically significant reduction in clinically significant exacerbations compared with omalizumab (RR=0.664, 95% credible interval (CrI) 0.513, 0.860). Mepolizumab was comparable with omalizumab for exacerbations requiring hospitalisation (RR=0.932, 95% CrI 0.350, 2.490) and forced expiratory volume in 1 second (FEV1; RR=0.645, 95% CrI -2.652, 3.959). The company notes that results should be treated with caution since many trial patients were not eligible for both treatments, and study populations differed in severity. Given the heterogeneity between the trials included in the NMA, the ERG considered that a random effects model would be more appropriate. A random effects NMA undertaken by the company indicates that the reduction in exacerbations is not statistically significant (RR=0.664, 95% CrI 0.283, 1.498). For exacerbations requiring hospitalisation, the treatment effect observed in the more restricted populations favours omalizumab but is not statistically significant. The company concluded that it is a reasonable assumption that, in patients who are eligible for both drugs, mepolizumab would be at least as effective as omalizumab.

3.1.8 Safety of mepolizumab

In the RCTs, the risk of eczema, nasal congestion and dyspnoea were potentially higher with mepolizumab than placebo. Adverse events (AEs) of special interest were: systemic, hypersensitivity and injection site reactions; cardiac events; infections; and malignancies. Infusion-related reactions were higher for IV (but not SC) mepolizumab than placebo whilst injection site reactions were higher for SC (but not IV) mepolizumab (8%) than placebo (3%). Hypersensitivity reactions, infections and malignancies occurred at similar rates for mepolizumab and placebo and there were no reports of anaphylaxis. Rates of all cardiac events were similar for mepolizumab and placebo, whilst rates of serious cardiac events were slightly higher for mepolizumab, though numbers were small. The incidence of the following serious AEs was higher for mepolizumab than placebo: herpes zoster (2 vs. none); hypertension (2 vs. none); and myocardial ischaemia (2 vs. none). There are few long-term safety data. In the RCTs and open-label studies, 5%-6% of patients on mepolizumab 100mg SC developed anti-mepolizumab antibodies, which the company claimed did not discernibly impact upon the pharmacokinetics and pharmacodynamics of mepolizumab in the majority of patients. Neutralising antibodies were detected in one subject.

3.2 Critique of the Clinical Evidence and Interpretation

The systematic review process followed by the company was comprehensive and the ERG was confident the searches were sufficient to identify all relevant studies of mepolizumab and omalizumab for inclusion in the review of clinical effectiveness. Although the ERG considered the evidence provided by the company to be generally of good methodological quality, there were a number of limitations and uncertainties in the evidence base which warranted caution in its interpretation.

3.2.1 Limitations of the trials

Patients were excluded from SIRIUS if they were unable to achieve a stable dose of OCS, which may not reflect clinical practice. Trial durations were relatively short (24 to 52 weeks). The primary outcome in DREAM and MENSA (clinically significant exacerbations) is a composite outcome including the requirement for systemic OCS (or double maintenance dose) and/or hospitalisation and/or ED visits.

3.2.2 Statistical justification for the sub-populations

The *post hoc* subgroup and modelling analyses used to justify the company's proposed populations should be interpreted with caution. Multivariate modelling of DREAM data showed that patients with a blood eosinophil count ≥150 cells/μL at screening had a ≥30% reduction in rate of exacerbations for mepolizumab vs. placebo; however, the uncertainty associated with the predicted rate reduction is not clear. The blood eosinophil threshold giving a 30% reduction in exacerbations varies between DREAM and MENSA and by number of previous exacerbations. The company's submission compares two options for a blood eosinophil threshold: ≥150/μL at screening or ≥300/μL in the previous 12 months.

3.2.3 Clinical validity of sub-populations

The company claims that the thresholds for eosinophil level and previous exacerbations were clinically plausible and practical to implement according to severe asthma specialists. In terms of eosinophil level, the European Medicines Agency concluded that eosinophil levels were not sufficiently predictive to justify a specific cut-off within their marketing authorisation. The ERG believed that the blood eosinophil count of ≥150 cells/μL at screening is not a valid criterion to find a population in which mepolizumab is more effective in the medium- and long-term for two reasons: 1) because 150/μL is, according to clinicians, within the normal range and; 2) because eosinophil levels can fluctuate. Due to the uncertainties around the subgroup analyses combined with the fact that a threshold of ≥300cells/μL in the previous 12 months was considered by clinicians and the committee to be more clinically relevant than ≥150/μL at screening, the former was used in the definition of the committee-preferred population. Clinical advisors to the ERG considered that a threshold of ≥4 previous exacerbations was clinically appropriate, and was consistent with NICE guidance for omalizumab which restricts the use of the drug to people requiring continuous or frequent treatment with oral corticosteroids (≥4 courses in the previous year).

3.2.4 Evaluation of the indirect comparison

The indirect comparison methods appeared broadly appropriate. However, the ERG considered that the results of the random effects model provided a more appropriate (and more conservative) estimate than those of the fixed effects model given the heterogeneity between trials. The company further acknowledged that the results should be treated with caution since only a small proportion of patients in the mepolizumab and omalizumab trials were eligible for both treatments, and study populations differed in terms of severity.

3.3 Cost-Effectiveness Evidence

The company conducted a systematic review on the cost-effectiveness of interventions for the treatment of severe eosinophilic asthma with mepolizumab. No suitable studies were found; therefore the company developed a *de novo* economic model, implemented in Microsoft Excel®, to estimate the cost-effectiveness of add-on mepolizumab compared with SoC and omalizumab.

The model employed a Markov cohort simulation approach. The perspective used was that of the NHS. The starting age of the cohort was set 50.1 years, the cycle length to four weeks and a lifetime time horizon was used. A discount rate of 3.5% per annum was used both for costs and utilities. The model includes four states: (i) on-treatment before continuation assessment; (ii) on-treatment after continuation assessment; (iii) off-treatment and; (iv) death. All patients on mepolizumab or omalizumab treatment enter the model in the 'on-treatment before continuation assessment' state, until the continuation assessment. After continuation assessment, patients transition either to 'on-treatment after

continuation assessment' or 'off-treatment' depending on whether or not they meet the continuation criteria: patients on mepolizumab continued on treatment unless the exacerbation rate worsened compared with the previous. Patients in the 'on-treatment after continuation assessment' state transition to the 'off-treatment' state when they discontinue treatment. Treatment discontinuation might happen either due to natural attrition or by reaching the end of the treatment duration, which in the base case was assumed to be 10 years. All patients on SoC enter the model in the 'off-treatment' state. During any cycle, patients can transition from any of the alive states to death as a consequence of either asthma-related mortality (ARM) following an exacerbation or due to other causes.

The effectiveness of mepolizumab was reflected in a reduction of exacerbation rates and in a better health-related quality of life (HRQoL). All exacerbation rates were initially calculated from the MENSA trial for both arms, mepolizumab and SoC. Different exacerbation rates were used before and after the continuation assessment to reflect the lower exacerbation rates of responders. The exacerbation rate for patients continuing on mepolizumab after the continuation assessment was assumed to be equal to that observed in patients meeting the continuation criteria during MENSA. The exacerbation rate for patients who discontinued mepolizumab was assumed to increase to that of patients on SoC.

The company's model assumed that ARM occurs only following a clinically significant exacerbation. In the base case analysis, the mortality rates after clinically significant exacerbations were based on two sources: Watson *et al*.[24] and the National Review of Asthma Deaths (NRAD) report.[7] The company assumed that the deaths reported in Watson *et al*. were those happening in hospital, which according to the NRAD report only account for the 30% of asthma-related deaths. Therefore, the total number of deaths was assumed to be 100/30 times greater than those reported in Watson *et al*. The probability of death after hospitalisation according to Watson *et al*. is 0.0038 for people aged 18 to 44 years and 0.0248 for people aged 45 years or older. After consultation, the company undertook a retrospective cohort analysis using the same database as the one used to inform Watson *et al*. (the CHKS database). but applying Roberts *et al*.'s age stratification: 45-54, 55-64 and ≥65.

Utility values were obtained from two sources. EQ-5D scores were captured at 4-weekly intervals in the DREAM trial. However, in the MENSA and SIRIUS trials, the SGRQ was used. The base case uses EQ-5D scores mapped from the SGRQ scores measured in the MENSA trial instead of the direct EQ-5D data captured within DREAM. The mapping from SGRQ scores to EQ-5D scores was performed using an algorithm proposed by Starkie *et al*.[25] to predict EQ-5D utility from the SGRQ in subjects with COPD. The company justified the use of SGRQ-mapped scores claiming "*EQ-5D did not capture the granularity in HRQoL of people with severe asthma*". Similarly to exacerbation rates, the company used different utility values before and after continuation assessment to reflect the higher HRQoL of responders. The utility value for patients on mepolizumab until continuation assessment was calculated based on all patients whilst the utility value for patients continuing mepolizumab after continuation

assessment was calculated based solely on the patients meeting the continuation criteria. The utility value for patients discontinuing mepolizumab after continuation assessment was assumed to drop to that of patients on SoC. During consultation, the company revealed that there was a baseline imbalance on the average EQ-5D values between patients on mepolizumab and SoC and presented baseline-adjusted utility values. Exacerbations were assumed to have an impact on the patients' HRQoL. The disutility values and their duration were based on a study by Lloyd *et al.*[26] For the duration of disutilities however, the company accepted after consultation to use the midpoint between the average exacerbation durations as measured in MENSA and the duration of the Lloyd *et al.*[26] study, as explained in Section 3.4.

As explained in Section 3.1, the company conducted an NMA to calculate the exacerbation RRs for mepolizumab and omalizumab compared with SoC. The resulting mean exacerbation RRs compared with SoC were 0.496 for mepolizumab and 0.746 and omalizumab. These RRs were applied only to the period before continuation assessment due to the differences in the continuation criteria between the two treatments: patients continued on mepolizumab unless the exacerbation rate worsened whilst patients on omalizumab continued only if they achieved a score of good or excellent in the global evaluation of treatment effectiveness (GETE). After continuation assessment, for mepolizumab the same exacerbation rate used in the base case was used, whilst for omalizumab the exacerbation rate observed in omalizumab responders during the INNOVATE trial [20] (0.373) was used.

The cost of mepolizumab used in the model included the Patient Access Scheme (PAS) proposed by the company. The list price reported in the British National Formulary (BNF)[27] was used for omalizumab, as directed by NICE, although a commercial-in-confidence PAS is in place. Instead of using the cost of the omalizumab treatment used in the recent omalizumab multiple technology assessment (MTA), [28] the company undertook a study to estimate the cost of the omalizumab treatment in clinical practice. The calculation of the average cost of the omalizumab treatment is not straightforward because the frequency and dosage of the injections depend on the patient's weight and serum IgE levels. The company-led study concluded that the annual cost of the omalizumab treatment was considerably higher (£11,370) than the one calculated based on the INNOVATE trial and used in the omalizumab MTA (£8,056). Unit costs for administration and monitoring costs were taken from the PSSRU,[29] and NHS Reference Costs 2013/2014,[30] whilst drug costs for SoC were taken from BNF. [27] Costs were updated when necessary to 2014 values using the health service cost index (HCHS).[29]

In their original base case analysis, the company estimated that the probabilistic incremental cost-effectiveness ratio (ICER) for add-on mepolizumab versus SoC was £19,511 per quality-adjusted life year (QALY) gained in their proposed population, and £15,478 per QALY gained in their proposed restricted population. As the appraisal progressed, the definition of the target population changed as did the PAS offered by the company, the continuation criteria, asthma-related mortality rates, exacerbation

rates and utility values, based to a large extent on the reasoning presented in Section 3.4. The final ICER presented by the company for add-on mepolizumab compared with SoC for the committee-preferred population and continuation criteria was £27,418 per QALY gained. All analyses in the company's submission used the PAS for mepolizumab.

Based on the list price for omalizumab, the company's analysis concluded that mepolizumab dominates omalizumab as it is estimated to be less expensive and more effective. Mepolizumab dominates omalizumab in all the sensitivity analyses undertaken by the company. The validity of this results is limited due to the existence of a PAS in place for omalizumab.

3.4 Critique of the Cost-Effectiveness Evidence and Interpretation

The mathematical model submitted by the company was conceptually reasonable and complete and had only a few minor implementation errors.

3.4.1 Continuation criteria

The original continuation criteria proposed by the company (i.e. continue on treatment unless the exacerbation rate increases compared to the previous year) implied that a subgroup of patients could remain on treatment even when experiencing no improvement. The company argued that some patients could benefit from a OCS dose reduction whilst maintaining asthma control. The appraisal committee consequently proposed continuation criteria as follows: a reduction of at least 50% in exacerbation rate and/or a clinically significant reduction in mOCS dose while maintaining or improving asthma control. The ERG noted that the ICERs calculated in the appraisal only reflected the cost-effectiveness of patients whose exacerbation rate was reduced at least 50%, since the effectiveness estimates were based on trials where an mOCS dose reduction was not allowed. The ERG notes that the ICER for mepolizumab versus SoC in patients whose mOCS dose is reduced but whose exacerbation rate is maintained is likely to be higher than that of patients whose exacerbation rate was reduced at least 50%. This is due to an important part of the treatment benefit coming from exacerbation reduction.

3.4.2 Inclusion of the mOCS users with <4 exacerbations in the proposed population

The difference in the estimated ICERs per QALY gained between the proposed population and the proposed restricted population suggest that the use of mepolizumab in mOCS users with <4 exacerbations may have a high ICER. In response to the ERG's clarification questions, the company undertook a scenario analysis for this sub-population that resulted in an ICER of £78,716 per QALY gained, based on the company's original analysis and original PAS price.

3.4.3 Exacerbation rates after continuation assessment

The exacerbation rates used in the model were calculated by dividing the number of exacerbations by the number of person-years of exposure in the MENSA trial. Those for patients continuing treatment after continuation assessment were calculated based on the data from Week 16 to the end of the trial (Week 32) in patients that met the continuation criteria at the end of MENSA. This is not ideal for three reasons: (i) the future rates of asthma observed in patients who met the continuation criteria (which was a non-worsening of the exacerbation rate) are likely to be higher than the rates observed due to regression to the mean; (ii) the exacerbation rate is measured during a short period (16 weeks), which results in uncertainty, and; (iii) measurements may be subject to potential inaccuracy due to the seasonal nature of asthma exacerbations. The ERG proposed instead to use the exacerbation rates observed in the COSMOS open label extension trial in patients who met the continuation criteria in MENSA and went on to participate in COSMOS. The appraisal committee agreed with this proposal and the company provided the relevant rates from COSMOS. The ERG also noted that patients on mepolizumab who did not meet the continuation criteria were by definition the most severe patients and therefore it was not reasonable to assume they would go on to have the average exacerbation rate observed in SoC. The committee agreed and the company provided the exacerbation rates of patients observed in COSMOS in patients who had failed the continuation criteria in MENSA, which were higher than those observed in SoC in MENSA.

3.4.4 Asthma-related mortality (ARM)

The company used ARM rates reported by Watson *et al*.[24] and the relative rates of ARM outside of hospital reported in the NRAD report.[7] The ERG noted that Watson *et al*. used a constant rate of ARM for those aged 45 years and over. However, the age stratification in Roberts *et al*. indicates that the rate of ARM is approximately six times higher in the 65 years and over group than that in the 45-54 years age group. The ERG noted that there is no evidence to believe this proportion was not applicable to severe asthma patients. Therefore, the ARM rate for those aged 45 years and over in Watson *et al.* is likely to overestimate mortality between the ages of 45 and 65 and underestimate it above the age of 65 years. This, in turn would overestimate the benefits of a reduction in ARM, as early deaths have a bigger impact than late deaths. After consultation, the company undertook a retrospective cohort analysis using the same database as the one used to inform Watson *et al*. but applying Roberts *et al*.'s age stratification: 45-54, 55-64 and ≥65. As expected, the mortality rate in the 45-54 age range was much lower (0.0092) than that in the ≥65 age range (0.0455). The ICERs for add-on mepolizumab compared with SoC as calculated by the company increased when using the ARM rates with the new age-stratification instead of that in Watson *et al*. [24]

3.4.5 Utility values

The company claimed that the EQ-5D suffered from a ceiling effect and poor sensitivity in severe asthma. Therefore, the company used an alternative instrument, the SGRQ, and mapped to the EQ-5D using an algorithm proposed by Starkie *et al.*[25] to predict EQ-5D utility from the SGRQ in subjects with COPD. The ERG noted that it is uncertain to what extent the mappings obtained using data from COPD rather than asthma could influence the results. Furthermore, if the mapping algorithm correctly predicts EQ-5D scores of patients with severe asthma, then the mapping would not address the claimed deficiencies of the EQ-5D. The ERG believed that the directly measured EQ-5D values were preferable to mapped EQ-5D estimates, with which the committee agreed. Therefore, directly measured EQ-5D values were used in the rest of the appraisal. In a similar way as with exacerbation rates, the company assumed that the utility value of those patients failing to meet the continuation criteria and discontinuing mepolizumab would drop to that of the average of patients on SoC. The ERG noted that the subgroup of patients failing the continuation criteria was likely to be the most severe subgroup and calculated the adjusted utilities for this subgroup based on the average utility for patients on mepolizumab and the average utility of patients on mepolizumab who met the continuation criteria.

3.4.6 Duration of disutility from exacerbations

The company assumed that the disutilities reflecting the impact on the HRQoL of exacerbations reported in Lloyd *et al.*[26] would last for 28 days, based on the length of the Lloyd *et al.*[26] study. The ERG considered that using the duration of the exacerbations as measured in MENSA would be more appropriate. The company argued then that the disutility due to an exacerbation could last longer than its measured length in terms of OCS burst or hospital stay. The ERG acknowledged that there is potential for the duration of the disutility from exacerbations to be underestimated using only the average length of exacerbations in MENSA. Consequently, the company and the ERG agreed that using the midpoint between the mean duration of exacerbations in MENSA and the length of the Lloyd *et al.*[26] study was a reasonable compromise.

3.4.7 OCS sparing

The company's submission included a scenario analysis that took into account the costs and consequences of long-term systemic OCS usage. This analysis had several limitations: (i) it used OCS sparing data from the ITT population of SIRIUS instead of the company's proposed or committee-preferred populations; (ii) it used OCS sparing estimates from SIRIUS whilst using exacerbation reductions observed in MENSA; (iii) the time horizon considered was 10 years instead of lifetime costs and utility decrement from fractures (resulting from osteoporosis) were not considered; (iv) some utility decrements estimated as chronic conditions were considered as one-off disutilities, and; (v) neither the proportion of the cohort that was alive at each cycle was considered to calculate the incidence of AEs nor the patients that suffered chronic disutilities from AEs that died were accounted for. The company

acknowledged and the ERG agreed that the company's analysis did not appropriately capture the long-term benefits of OCS reduction.

3.4.8 Comparison with omalizumab

The cost of omalizumab used within the MTA was considered by the ERG to be more appropriate than that of the company's study because it resulted in costs and efficacy data deriving from the same source. The ERG noted that the NICE guidance recommends omalizumab only for patients on "continuous or frequent treatment with oral corticosteroids"[28]. The ERG believes that omalizumab should be compared to mepolizumab in the population in which omalizumab is recommended. The company used the exacerbation RR of omalizumab for the ITT population (0.373) instead of the one reported for the mOCS subgroup (0.293).[31] Finally, the ERG believed that using a random effects model to calculate the exacerbation RR for patients before continuation assessment was more appropriate for the NMA than the fixed effects model used by the company.

3.5 Additional Work Undertaken by the Evidence Review Group

The ERG undertook additional analyses using different assumptions to those made by the company in their base case. These analyses informed the AC and led to new analyses by the company. The list of alternative assumptions used by the ERG that were incorporated to the company's revised base case is as follows:

1) Using the exacerbation rates observed in the COSMOS open-label extension study for patients on mepolizumab after continuation assessment.
2) Use of directly measured EQ-5D scores instead of the scores mapped from SGRQ;
3) Use of alternative ARM rates. First using the rates combining the data from Watson *et al.*[24] and Roberts *et al.*[32] and after consultation using those calculated in the company's retrospective cohort study;
4) Using the duration of disutility due to exacerbations equal to the mid-point of the length of exacerbations measured in MENSA and the length of the Lloyd *et al*.[26] study.

The ERG applied the following changes to the company's revised base case:

1) Use of age-adjusted utilities, as per Ara and Brazier.[33]
2) Use of the attrition rate calculated on the committee-preferred population instead of ITT population.
3) Use of average age at start from committee-preferred population (51.5 years) instead of ITT population (50.1 years).

4) Use of the correct percentage of patients meeting the continuation criteria in the committee-preferred population (the company had made a minor error which was acknowledged upon clarification request).

After applying these changes to the company's revised base case, the ICER for mepolizumab compared with SoC increased from £27,418 to £29,163 per QALY gained. These ICERs were calculated based on continuation criteria according to which patients on mepolizumab would discontinue treatment after one year unless their number of exacerbations was reduced by at least 50% or their mOCS dose was reduced whilst maintaining asthma control. However, patients were not allowed to reduce their mOCS dose in the trials that served as evidence source for the treatment efficacy. Therefore, the ICER for patients who fail to achieve a 50% reduction in the number of exacerbations but continue on treatment due to a reduction in mOCS dose whilst maintaining asthma control is uncertain. The ERG estimated the ICER of mepolizumab versus SoC for these patients to be £60,825 per QALY, by assuming that these patients would have the same reduction in exacerbations as that observed in the MENSA RCT in patients on SoC (50.4%). This ICER does not take the benefits of avoiding long-term mOCS side-effects into account, but the ERG notes that it is unlikely that taking these benefits into account would drive the ICER under the threshold of £30,000 per QALY.

The ERG undertook exploratory analyses assessing the impact of different continuation criteria, different average age at treatment start and a potential waning effect. The ICER for mepolizumab compared with SoC increased from £29,163 to £31,378 and to £31,895 per QALY, when the continuation criterion threshold for reduction in exacerbations was lowered from 50% to 30% and 0% respectively. The ERG argued that if mepolizumab were to be recommended, the average age at treatment start would be lower than that observed in the trials because patients would start on mepolizumab soon after their asthma was uncontrolled in step 4 (high dose ICS plus additional maintenance treatments and short courses of OCS). The ERG estimated that the ICER of mepolizumab would increase from £29,163 to £32,557 and to £39,761 per QALY if the average age at treatment initiation was 45 and 40 years respectively instead of the 51.5 years observed in the trial. The AC considered a hypothetical waning effect in the treatment efficacy. The company argued that there was no evidence of a waning effect and that the mechanism of action of the drug did not justify a waning effect. However, in the absence of long term effectiveness data, the ERG presented results of exploratory analyses that showed that the ICER of add-on mepolizumab versus SoC would increase from £29,163 to £34,744 and to £43,429 per QALY if treatment effect was assumed to wane linearly until losing all its effect in 30 and 10 years respectively.

3.6 Conclusions of the Evidence Review Group Report

The evidence submitted by the company is consistent with the NICE scope for interventions, comparators and relevant outcomes. The ERG was satisfied that the final definition of the relevant population included the blood eosinophil count of ≥300 cells/µl in the previous year instead of the ≥150 cells/µL at screening. The criterion of ≥4 exacerbations in the previous year appeared more clinically robust than a dependency on mOCS.

The ERG noted that the AC shared its preference for using the exacerbation rates from the COSMOS extension study as well as that it adopted the adjustments in the exacerbation rates and utilities for non-responders and the mortality rates based on more accurate age stratification. However, the ERG noted that the ICERs used by the AC in its decision to recommend add-on mepolizumab were based on part of the relevant population only. The continuation criteria establish that patients who have not achieved a 50% reduction in the number of exacerbations can still continue on treatment if their dose of mOCS is reduced whilst maintaining asthma control. However, the trials in which the treatment effect was measured did not allow a reduction in mOCS dose. The ERG believes that the ICER for this subgroup is higher than that reflected in the FAD.

4. Key Methodological Issues

The best way to define the relevant population in terms of severity of asthma and degree of eosinophilia was unclear. The severity of asthma was defined by the company in terms of number of exacerbations in the previous year and/or dependency on mOCS. The company argued that patients on mOCS were especially severe cases regardless of the number of exacerbations. The ERG noted that mepolizumab was likely to be less cost-effective in patients on mOCS who had less than 4 exacerbations in the previous year. The level of eosinophilia was defined by the company using a blood eosinophil count of ≥150 cells/µl at screening. The ERG, advised by its clinical experts, argued against this criterion because blood eosinophil levels fluctuated over time and a level of blood eosinophil count of ≥150 cells/µl is well within the normal range. Consequently, the AC preferred to use a level of blood eosinophil count of ≥300 cells/µl in the previous year to define the relevant population.

The company's economic model was based on an analysis of responders and non-responders. The company assumed that non-responders would have a disease progression similar to those on SoC. However, the ERG pointed out that if the responders are individuals with a better prognosis, then the non-responders would have a worse prognosis than the average patient in the control arm. The ERG consequently applied adjustments for the exacerbation rates and the utilities of non-responders.

The company tried to include the benefits of mOCS sparing in their model. It is well known that the long-term use of mOCS has important side effects. However, it is difficult to capture these side effects, as they affect the likelihood of a patient developing a myriad of conditions. The company included

cataracts, myocardial infarction, peptic ulcer and osteoporosis in their analysis, but these are only a subset of the conditions affected by the long term use of mOCS. In addition, it is complicated to estimate how a partial reduction of the mOCS dose affects the incidence of these side effects. Further research on this topic would be of high interest given the prevalence of OCS in current practice.

Finally, the continuation criteria included a condition that was not observed in the trials used to estimate treatment efficacy, i.e. the reduction in mOCS dose. In the absence of evidence on how the reduction of mOCS would affect the treatment effect in these trials, the ERG and the AC were forced to estimate the ICER for this subgroup based on other trials.

5. National Institute for Health and Care Excellence Guidance

In December 2016, following three AC meetings, on the basis of the evidence available (including verbal testimony of invited clinical experts and patient representatives), the AC produced guidance that add-on mepolizumab was recommended as an option for treating severe refractory eosinophilic asthma in adults, only if the blood eosinophil count is ≥300 cells/µl in the previous 12 months; and the patient has had 4 or more exacerbations in the previous year or has been on mOCS over the previous 6 months. The AC established that mepolizumab should be discontinued unless the number of exacerbations was reduced by ≥50% or a clinically significant reduction in mOCS use was achieved while maintaining or improving asthma control. The recommendation was conditional on the company providing mepolizumab with the agreed PAS.

5.1 Consideration of Clinical and Cost-Effectiveness Issues Included in the Final Appraisal Determination

The full list of the issues considered by the Appraisal Committee can be found in the FAD.[34] The key issues are described in the following sections.

5.1.1 Current Clinical Management

The AC considered the current clinical management of severe eosinophilic asthma in England and noted that it follows guidelines from the British Thoracic Society and Scottish Intercollegiate Guidelines Network (SIGN). The clinical experts explained that the management of severe eosinophilic asthma lies within what was previously known as step 4 and step 5 of the superseded 2014 version of the British Thoracic Society and SIGN guidelines. The current guidelines (2016) indicate that those people having high-dose therapies (previously step 4) or continuous or frequent use of oral steroids (previously step 5) should be referred for specialist care. The AC understood that oral systemic corticosteroids are used either for short periods to manage an exacerbation, or for longer periods as maintenance treatment when it is difficult to wean people off corticosteroids without an increase in exacerbations. The AC concluded that in clinical practice in the NHS, people with severe refractory eosinophilic asthma who have adhered

to an optimised standard treatment plan (that is high-dose therapies [previously step 4], or continuous or frequent use of oral corticosteroids [previously step 5]) might be offered mepolizumab by a specialist.

5.1.2 Uncertainties in the Clinical evidence

The AC concluded that the comparison of mepolizumab with omalizumab was not clinically relevant or methodologically robust and therefore did not consider this comparison further.

5.1.3 Uncertainties in the Economic Modelling

The AC noted that the ICER was higher when the age of onset of treatment was lower. The AC concluded that there was some evidence to suggest that the age of onset of treatment was lower than the company's estimate and agreed to take this into account when making its decision.

The committee recognised the challenges in modelling the benefits of reducing mOCS, and therefore also a related continuation rule.

6. Conclusion

The NICE AC considered the ERG's ICER of £29,163 per QALY, but acknowledged that the ICER would be higher (£32,557 per QALY), if patients were younger (45 years) at treatment start than the mean age in the relevant subgroup in the trial (51.5 years), or lower if the adverse effects associated with the long-term use of systemic corticosteroids were accounted for. The AC therefore concluded that mepolizumab, as an add-on to SoC, could be recommended as an option for treating severe refractory eosinophilic asthma in adults who had had 4 or more exacerbations in the previous year and/or dependency on mOCS, and a blood eosinophil count of ≥300 cells/µl in the previous year, if patients discontinued treatment after a year unless a reduction in the number of exacerbations of at least 50% was achieved or systemic corticosteroids use was reduced whilst maintaining asthma control.

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Author contributions

Katy Cooper, Sue Harnan, and Christopher Carroll critiqued the clinical effectiveness data reported by the company. Iñigo Bermejo and Matt Stevenson critiqued the mathematical model provided and the cost-effectiveness analyses submitted by the company. Jean Hamilton critiqued the network meta-analysis performed by the company. Mark Clowes critiqued the literature searches conducted by the company. Tim Harrison and Shironjit Saha provided clinical advice to the ERG throughout the project. All authors were involved in drafting and commenting on the final document. Iñigo Bermejo acts as the guarantor of the manuscript. This summary has not been externally reviewed by PharmacoEconomics.

Compliance with Ethical Standards

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Conflicts of Interest

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