NICE National Institute for Health and Care Excellence

Fast Track Appraisal

Mepolizumab for treating severe eosinophilic asthma [ID3705]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

FAST TRACK APPRAISAL

Mepolizumab for treating severe eosinophilic asthma [ID3750]

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission** from GlaxoSmithKline
2. **Company response to NICE's request for clarification**
3. **Patient group, professional group and NHS organisation submission** from:
   a. Asthma UK
4. **Expert personal perspectives** from:
   a. Prof. Ian Pavord, Professor of Respiratory Medicine – clinical expert, nominated by GlaxoSmithKline
   b. Peter McQuitty – patient expert, nominated by Asthma UK and British Lung Foundation Partnership
   c. Lottie Renwick, Senior Policy Officer – patient expert, nominated by Asthma UK and British Lung Foundation Partnership
5. **Evidence Review Group report** prepared by PenTAG
6. **Evidence Review Group – factual accuracy check**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Fast track appraisal: cost-comparison case

Mepolizumab: Asthma (eosinophilic, severe) – (review of TA431) [ID3750]

Document B

Company evidence submission

21st May 2020

File name	Version	Contains confidential information	Date
[ID3750]_Mepolizumab_FTA_NICE Submission_Document B_[redacted]	**1.0**	**Yes**	**21st May 2020**

Contents

Tables and figures

Tables

Figures

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

B.1.1 Decision problem

B.1.1.1 Population

The purpose of this guidance review is to align the mepolizumab reimbursed population to that recommended by NICE for benralizumab (TA565). This submission focuses on the part of the severe asthma population reimbursed for reslizumab and benralizumab, but not currently reimbursed for mepolizumab, that is, patients with a blood eosinophil count of ≥400 cells per microlitre and who have had ≥3 severe asthma exacerbations in the previous 12 months (Table 1).

The published NICE technology appraisal guidance for the comparator(s) specified in the NICE scope recommends reslizumab and benralizumab for a subgroup of the population within the respective marketing authorisations, and, therefore, a cost-comparison case can be made only for these subpopulations.

For mepolizumab (TA431[1]), the current recommendation is:

Mepolizumab, as an add-on to optimised standard therapy, is recommended as an option for treating severe refractory eosinophilic asthma in adults, only if:

- The blood eosinophil count is 300 cells/microlitres or more in the previous 12 months and
- the person has agreed to and followed the optimised standard treatment plan and
- has had 4 or more asthma exacerbations needing systemic corticosteroids in the previous 12 months or
- has had continuous oral corticosteroids (OCS) of at least the equivalent of prednisolone 5 mg per day over the previous 6 months and
- the company provides the drug with the discount agreed in the patient access scheme

For reslizumab (TA479[2]), the current recommendation is:

As an add-on therapy, reslizumab is recommended as an option for the treatment of severe eosinophilic asthma that is inadequately controlled in adults despite maintenance therapy with high-dose inhaled corticosteroids plus another drug, only if:

- the blood eosinophil count has been recorded as **400 cells per microlitre** or more
- the person has had **three or more severe asthma exacerbations** needing systemic corticosteroids in the past 12 months and
- the company provides reslizumab with the discount agreed in the patient access scheme

For benralizumab (TA565[3]), the current recommendation is:

As an add-on therapy, benralizumab is recommended as an option for treating severe eosinophilic asthma that is inadequately controlled in adults despite maintenance therapy with high-dose inhaled corticosteroids and long-acting β-agonists, only if:

- The person has agreed to and followed the optimised standard treatment plan and
- the blood eosinophil count has been recorded as **300 cells per microlitre** or more and the person has had **four or more exacerbations** needing systemic corticosteroids in the previous 12 months, or has had **continuous OCS** of at least the equivalent of prednisolone 5 mg per day over the previous 6 months (that is, the **person is eligible for mepolizumab**) or
- the blood eosinophil count has been recorded as 400 cells per microlitre or more with **three or more exacerbations** needing systemic corticosteroids in the past 12 months (that is, the **person is eligible for reslizumab and not eligible for mepolizumab**)

Benralizumab is recommended only if the company provides it according to the commercial arrangement.

These populations have been recommended by NICE as it optimises the cost effectiveness of the medicines in patients with severe asthma.

With this submission, the company is seeking to have the mepolizumab population updated in line with the current reimbursed populations for benralizumab (TA565) as follows:

Mepolizumab, as an add-on to optimised standard therapy, is recommended as an option for treating severe refractory eosinophilic asthma in adults, only if:

- The person has agreed to and followed the optimised standard treatment plan and
- the blood eosinophil count has been recorded as **300 cells per microlitre** or more and the person has had **four or more exacerbations** needing systemic corticosteroids in the previous 12 months, or has had **continuous OCS** of at least the equivalent of prednisolone 5 mg per day over the previous 6 months or
- the blood eosinophil count has been recorded as 400 cells per microlitre or more with **three or more exacerbations** needing systemic corticosteroids in the past 12 months (that is, the **person is eligible for reslizumab)**

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People 6 years and older with severe refractory eosinophilic asthma	People 6 years and older with severe refractory eosinophilic asthma	
Intervention	Mepolizumab	Mepolizumab	
Comparator(s)	For people with severe asthma for whom biologics are indicated and recommended according to NICE guidance: • Reslizumab • Benralizumab For people with severe asthma for whom currently available biologics are not indicated and suitable: • Optimised standard therapy without biologics	**Comparator 1:** Reslizumab (Cinqaero®) 10 mg/mL concentrate for solution for infusion **Comparator 2:** Benralizumab (Fasenra®) 30 mg Available as: solution for injection in pre-filled pen and solution for injection in pre-filled syringe	GSK proposes an FTA for mepolizumab as it is likely to provide similar or greater health benefits at similar or lower cost than technologies already recommended in technology appraisal guidance for the same indication Both the committee and the ERG for TA565 (benralizumab) concluded that both mepolizumab and benralizumab have similar clinical effectiveness and are cost-effective for the eligible populations using the MAIC provided by the company. The company's MAIC compared mepolizumab and benralizumab only The company submission for TA565 did not present data comparing benralizumab to reslizumab and instead assumed that both treatments had the same efficacy for the analyses. In the ERG analysis, benralizumab was deemed cost effective when compared with reslizumab. The equivalent efficacy assumption for benralizumab and reslizumab resulted in benralizumab

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			achieving a wider recommendation than mepolizumab **Based on the points above and GSK's published ITC showing comparable efficacy[4], GSK will provide cost minimisation analyses for both benralizumab and reslizumab**. For reslizumab, additional study efficacy data is provided as this addresses the efficacy evidence gap for the comparison of mepolizumab with reslizumab as a robust efficacy comparison was not provided in the benralizumab appraisal
Outcomes	The outcome measures to be considered include: • asthma control • incidence of clinically significant exacerbations, including those that require unscheduled contact with healthcare professionals or hospitalisation • use of oral corticosteroids • patient and clinician evaluation of response • lung function • mortality • time to discontinuation • adverse effects of treatment	The outcome measures to be considered include the outcome measures utilised in the ITC: • Asthma control • Incidence of clinically significant exacerbations, including those that require unscheduled contact with healthcare professionals or hospitalisation • Lung function	An FTA is proposed as the medicines have all been appraised by NICE. The analysis will focus on the key clinical outcomes to compare mepolizumab against comparators.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• health-related quality of life		
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life-year. 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 Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.	As this will be an FTA submission, a cost-comparison analysis will be used. There will not be an economic model.	The FTA template will be completed for this submission. This will include a cost-comparison analysis of mepolizumab, reslizumab and benralizumab. The analysis will include acquisition costs and administration costs for the respective technologies.
Abbreviations: ERG; Evidence Review Group, FTA; fast track appraisal, GSK; GlaxoSmithKline, ITC; indirect treatment comparison, MAIC; matching-adjusted indirect comparison, NHS; National Health Service, NICE; National Institute for Health and Care Excellence, TA; technology appraisal			

B.1.2 Description of the technology being appraised

Table 2 Technology being appraised: mepolizumab

UK approved name and brand name	**Brand name:** Nucala ▼ **Generic name:** Mepolizumab **Approved name:** There are three formulations of mepolizumab: 1) Nucala 100 mg powder for solution for injection 2) Nucala 100 mg solution for injection in pre-filled pen 3) Nucala 100 mg solution for injection in pre-filled syringe[5]
Mechanism of action	Mepolizumab is a humanised monoclonal antibody (IgG1, kappa), which targets human IL-5 with high affinity and specificity. IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation and survival of eosinophils. 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.[5]
Marketing authorisation/CE mark status	European marketing authorisation was granted on 1 December 2015.[5] European marketing authorisation for use in paediatric patients was granted on 30 August 2018.[6] European marketing authorisation for self-administration using pre-filled pen or pre-filled syringe was granted on 1 August 2019.[7]
Indications and any restriction(s) as described in the SmPC	Nucala is indicated as an add-on treatment for severe refractory eosinophilic asthma in adults, adolescents and children aged 6 years and older. Note that the pre-filled pen and syringe are not indicated for children aged 6–11 years. Only the mepolizumab powder for solution for injection is indicated in children 6–11 years of age. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SmPC.[5]
Method of administration and dosage	Nucala should be prescribed by physicians experienced in the diagnosis and treatment of severe refractory eosinophilic asthma. The recommended dose of mepolizumab is administered subcutaneously once every 4 weeks. Mepolizumab is intended for long-term treatment. 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.[5]
Additional tests or investigations	No additional tests or investigations are necessary to identify the population for whom mepolizumab is indicated. Severe asthma patients are already phenotyped in a specialist setting. A blood test for eosinophil levels is required to identify those patients that are likely to experience a clinically significant response to mepolizumab, and this already forms part of the routine assessment of patients during screening for severe asthma. Mepolizumab powder for solution for injection will be administered in a specialist setting, most likely by a specialist respiratory nurse. Mepolizumab requires reconstitution with 1.2 mL of sterile water, typically complete within approximately 5 minutes. Appropriate facilities already exist for the administration of omalizumab (a biologic for severe allergic, IgE-driven asthma). However, increased capacity as a result of increasing demand from patients deemed eligible for mepolizumab may need to be addressed. Monitoring requirements for mepolizumab directly following administration will be driven by locally led protocols. Although there is no formal requirement in the SmPC, in mepolizumab clinical trial protocols patients were monitored for 1 hour following administration.[8] The pre-filled formulations for mepolizumab (100 mg solution for injection in pre-filled pen or syringe) are also licensed and available for self-administration by the patient or caregiver.
List price and average cost of a course of treatment	Mepolizumab is intended for long-term treatment. The need for continued therapy should be considered on at least an annual basis as determined by a physician assessment of the patient's disease severity and level of control of exacerbations. In practice, patients on mepolizumab may be assessed at more regular intervals in line with local treatment protocols. Cost of a year of treatment every 4 weeks (excluding administration costs): List price: £840 × 13 administrations = £10,920
PAS/commercial arrangement (if applicable)	There is a confidential simple discount PAS for Nucala PAS net price: [redacted]
Abbreviations: IgE; immunoglobulin E, IgG; immunoglobulin G, IL-5; interleukin-5, PAS; patient access scheme, SmPC; summary of product characteristics	

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Severe asthma

Asthma is a chronic heterogeneous lung disease characterised by inflammation, narrowing of the airways and reversible airway obstruction. The majority of patients with asthma can be adequately controlled by following step-wise treatment recommendations as stated in the British Thoracic Society (BTS)/Scottish Intercollegiate Guideline Network (SIGN) British Guideline on the Management of Asthma.[10] However, a minority of patients (approximately 5%) experience uncontrolled asthma despite attempts to control their disease.[11] A task force, supported by the European Respiratory Society and American Thoracic Society, state that when a diagnosis of asthma is confirmed and co-morbidities have been addressed, severe asthma is defined 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”.[12] The uncontrolled subjects of the above definition are classified as refractory.

Around 155,000 people in the UK have severe asthma.[13] This is a debilitating form of the condition that does not respond to usual treatments. This group of high-risk patients may suffer from frequent exacerbations, limited control of symptoms and compromised quality of life (QoL) from both their asthma and as a result of treatment-related side effects.[12] Exacerbations are particularly disabling for patients, and typically require treatment with systemic corticosteroids and may require hospital admission. Despite current treatments, asthma patients are at increased risk of death. One of the strongest predictors of death due to asthma is asthma-related hospitalisation (including hospitalisation as a result of an exacerbation).[14,15] In 2016/17 there were 65,442 hospital admissions due to asthma in the UK. This links with the fact that patients with severe asthma are also the heaviest users of health services. Asthma hospital admissions cost National Health Service (NHS) England £133M in 2016/17.

In addition, severe asthma clinics within the UK are working over capacity with long waiting lists, consequently limiting patient access to biologic treatment that can help reduce asthma exacerbations.

Furthermore, many general practitioners are not spotting the warning signs of severe asthma, including frequent severe asthma attacks. In fact, an estimated 80% of eligible patients are not being treated with a specialist biologic medicine for severe asthma.[12]

B.1.3.2 Severe refractory eosinophilic asthma

Evidence shows that once a correct diagnosis of asthma has been made, co-morbidities addressed and therapy ‘optimised’, patients with severe asthma are comprised of complex, overlapping and non-overlapping phenotypes, and one example of such is the severe eosinophilic asthma phenotype.[12] Studies in the severe asthma population have shown that more than half of these patients have persistent eosinophilic airway inflammation despite high-dose ICS.[16,17] Eosinophilic

asthma can be associated with increased asthma severity, late-onset disease, and a refractory response to even high doses of ICS that requires treatment with parenteral or oral steroids.[18,19] Eosinophilic asthma inflammation can be measured in both blood and sputum, but studies have confirmed that late-onset severe refractory eosinophilic asthma can be reliably characterised by establishing blood eosinophil thresholds in the presence of high-dose ICS in a poorly controlled exacerbating phenotype.[20,21]

B.1.3.3 Clinical care pathways

Severe asthma is defined as “asthma that requires treatment with high-dose ICS plus a second controller and/or systemic corticosteroids to prevent it from becoming ‘uncontrolled’ or that remains ‘uncontrolled’ despite this therapy.”[10,12] Some patients with severe asthma are not controlled with high-dose ICS plus another controller such as a long-acting β-agonists (LABAs), leukotriene receptor antagonists, tiotropium (adults only) or theophyllines. These patients may continue to suffer poor asthma control and asthma exacerbations, and may require regular long-term to achieve adequate control. Patients prescribed OCS should already be under the care of a specialist asthma service (see Figure 1).[10,12] Previously, OCS were the only option for asthmatics not controlled by high-dose ICS plus other controllers. However, for severe allergic asthmatics with recurrent exacerbations, the anti-immunoglobulin E (IgE) monoclonal antibody omalizumab is available. The interleukin-5 (IL-5)-targeting therapies mepolizumab and reslizumab were both approved by NICE in 2017 for severe refractory eosinophilic asthma. Additionally, benralizumab, an anti-IL5 receptor monoclonal antibody, was recommended by NICE in 2019.

B.1.3.4 Anti-IgE monoclonal antibody

The BTS/SIGN guideline also refers to omalizumab (Xolair, a humanised monoclonal antibody that binds to circulating IgE, reducing levels of free serum IgE), which targets a different pathway to mepolizumab as a steroid-sparing agent for patients at Step 5 (Specialist Therapies). This is consistent with the NICE pathway for asthma. In 2013 NICE completed a multiple technology appraisal (MTA; technology appraisal [TA] 278) for omalizumab, and recommended it as a treatment option for treating severe persistent confirmed atopic IgE mediated asthma, as an add-on to optimised standard therapy in patients ≥6 years who need continuous or frequent treatment with OCS (defined as four or more courses in the previous year) (along with an approved confidential patient access scheme).[22]

B.1.3.5 Anti-IL-5 monoclonal antibody

The BTS/SIGN guideline also recommends the use of anti-IL-5 monoclonal antibodies in eligible patients with a high OCS burden. Patients being considered for monoclonal antibody treatment should be assessed to confirm the diagnosis of asthma, that uncontrolled asthma is the cause of their ongoing symptoms and that they are adherent with current treatment. An asthma specialist with expertise in monoclonal antibody treatment should assess patients prior to treatment, and treatment should take place in a specialist centre with the appropriate resources and training, including access to an intensive care unit.[10]

BTS/SIGN have based their recommendations on evidence from a systematic review of anti-IL-5 monoclonal antibody therapies, which reported reduced asthma exacerbation rates and emergency department/unscheduled care visits with mepolizumab and benralizumab, and reduced asthma exacerbation rates with reslizumab, compared with placebo. No serious excess adverse events were reported, although significantly more patients receiving benralizumab than placebo discontinued treatment due to adverse events, and this requires further investigation. Mepolizumab has also demonstrated significant glucocorticoid-sparing effect reductions in exacerbation as well as improved QoL. However, BTS/SIGN acknowledge that there is a lack of head-to-head trials comparing mepolizumab and other IL-5 therapies. Therefore, head-to-head studies are needed to confirm the relative clinical and cost effectiveness of each approach. The BTS/SIGN recommendations are consistent with the NICE pathway for mepolizumab, reslizumab and benralizumab (see details below).[10]

B.1.3.6 Mepolizumab

In 2017 NICE completed a STA (TA431) for mepolizumab and recommended it as an add-on to optimised standard therapy, as an option for treating severe refractory eosinophilic asthma if the blood eosinophil count is ≥300 cells/μL in ≥12 months and has had ≥4 or more exacerbations needing systemic corticosteroids in ≥12 months, or has had continuous OCS of at least the equivalent of prednisolone 5 mg per day for ≥6 months and the company provides the drug with the discount agreed in the patient access scheme (PAS).[1]

B.1.3.7 Reslizumab

In 2017 NICE completed a STA (TA479) for reslizumab and recommended it as an add-on therapy for severe eosinophilic asthma that is inadequately controlled in adults despite maintenance therapy with high-dose ICS plus another drug, only if the blood eosinophil count has been recorded as ≥400 cells/μL, the person has had ≥3 severe asthma exacerbations needing systemic corticosteroids in ≥12 months and the company provides reslizumab with the discount agreed in the PAS.[2]

B.1.3.8 Benralizumab

In 2019 NICE completed a STA (TA565[3]) for benralizumab and recommended it as an add-on therapy in patients with severe eosinophilic asthma that is inadequately controlled in adults despite maintenance therapy with high-dose ICS and LABAs, only if the person has agreed to and followed the optimised standard treatment plan, the blood eosinophil count has been recorded as ≥300 cells/μL and the person has had ≥4 exacerbations needing systemic corticosteroids in the previous 12 months, or has had continuous OCS of at least the equivalent of prednisolone 5 mg per day over the previous 6 months (that is, the person is eligible for mepolizumab) or the blood eosinophil count has been recorded as ≥400 cells/μL with ≥3 exacerbations needing systemic corticosteroids in the past 12 months. Benralizumab is recommended only if the company provides it according to the commercial arrangement.

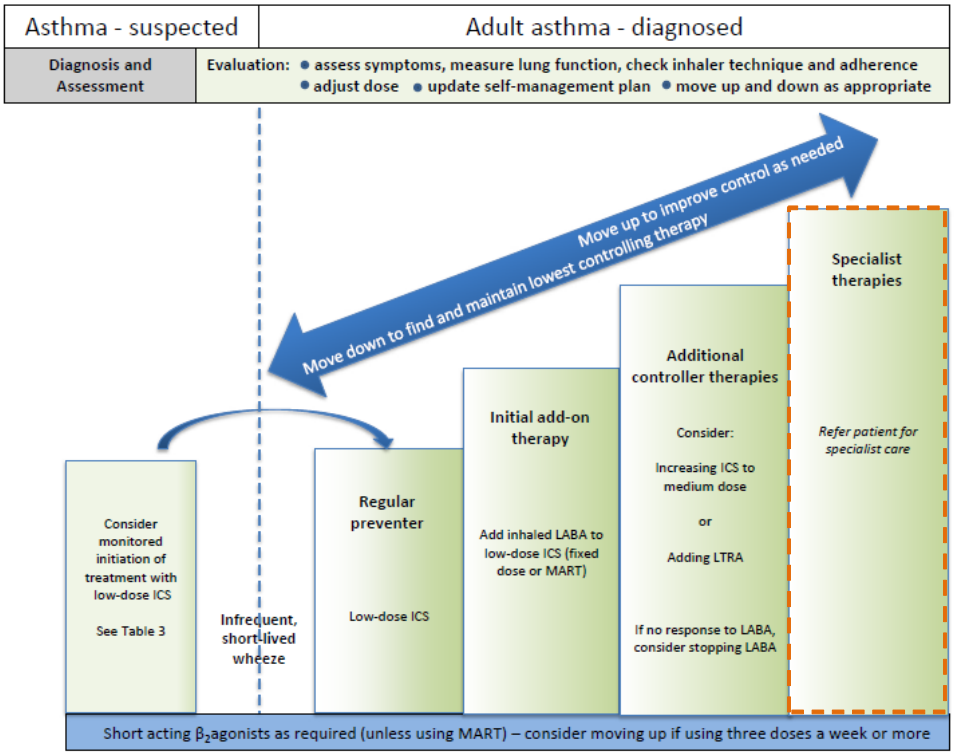
Therefore, guidance on the use of mepolizumab, reslizumab and benralizumab differs in England/Wales and Scotland and the relevant NICE or summary of product

characteristics advice should be checked prior to considering these treatment approaches.[3]

B.1.3.9 Other agents

The BTS/SIGN guideline also refers to other available treatments and steroid-sparing treatments. Other available treatments including immunosuppressants such as methotrexate,[23,24] cyclosporine[25,26] and oral gold[27] have demonstrated variable and marginal effects on OCS reduction but with significant toxicity. BTS/SIGN only recommend the above immunosuppressants as a 3-month trial, and only if other drug treatments have been proven unsuccessful.[10] Bronchial thermoplasty is also considered a treatment option for adult patients who have poorly controlled asthma despite optimal therapy. However, the BTS/SIGN guideline suggests this results in a modest improvement in asthma QoL in the year after treatment, and produces no consistent improvement in asthma symptoms or forced expiratory volume in 1 second.[10]

Figure 1 BTS/SIGN Summary of management in adults



Abbreviations: BTS; British Thoracic Society, ICS; inhaled corticosteroids, LABA; long-acting β-agonist, LTRA; leukotriene receptor antagonist, MART; maintenance and reliever therapy, SIGN; Scottish Intercollegiate Guidelines Network

B.1.4 Equality considerations

Mepolizumab is indicated as an add-on treatment for severe refractory eosinophilic asthma in adults, adolescents and children aged 6 years and older. The current NICE recommended population for mepolizumab is in adults. However, this recommended population is extrapolated to the paediatric population through the

NHS England Policy for Commissioning Medicines for Children in Specialised Services.[28]

B.2 Key drivers of the cost effectiveness of the comparator(s)

B.2.1 Clinical outcomes and measures

Table 3 Summary of clinical outcomes and measures applied to assess cost effectiveness

	Outcome	Measurement scale	Used in cost-effectiveness model?	Impact on ICER*	Committee's preferred assumptions	Uncertainties
Reslizumab NICE TA479[2]	Reduction in oral corticosteroid use	Reduction in oral corticosteroid use	No	The potential benefits of a reduction in the use of oral corticosteroids were not included in the economic analysis. The ICER would have been lower, as there would be QALY gains through an improvement in health-related quality of life.	The committee concluded that, had the potential benefits of oral corticosteroid sparing been included in the economic analysis, the most plausible ICER for reslizumab could be slightly lower.	Limited data on the health-related quality of life (HRQoL) associated with the reduction in use of oral corticosteroids
	Upward adjustment in the exacerbation rate of the SoC arm	Baseline rate of exacerbations	Yes	A higher and adjusted baseline exacerbation rate in the SoC arm would lead to a larger comparative reduction in exacerbation rate	The committee noted the company's evidence supporting higher exacerbation rates than seen in the clinical trials (4.85 vs 2.68). They concluded that the most robust estimate of	

				seen with reslizumab and, hence, a greater difference in incremental QALYs, which would result in a lower ICER	relative effectiveness was derived from the exacerbation rates in the clinical trials and that unadjusted baseline exacerbations was the best available data for decision-making.	
	Stopping rule for treatment	When treatment is stopped	Yes	The company showed that there was minimal difference in cost effectiveness for reassessment at 16 weeks, 6 months or 52 weeks of treatment. There was minimal effect on the ICER.	The committee concluded that reassessment at 12 months was the most appropriate and there was minimal difference to the ICER observing earlier timeframes. There was no rule for stopping treatment with reslizumab in the economic model and clinical experts stated that if patients continued to benefit from treatment, they would remain on reslizumab indefinitely	
	Lower mean duration for a severe exacerbation in the reslizumab arm compared with standard care	Utility value	Yes	Increased utility associated with shorter periods in the severe health state for patients on active therapy, resulting in higher QALYs. There	A higher utility value was applied to the severe exacerbation state for reslizumab as the exacerbation duration was longer in the best supportive care cohort. The committee noted the effect on cost	ERG highlighted uncertainty to these estimates as there was a lack of robust HRQoL data.

				was minimal effect on the ICER.	effectiveness was minor, but it was considered acceptable	
Benralizumab NICE TA565[3]	Reduction in oral corticosteroid use	Reduction in oral corticosteroid use	Yes	The potential benefits of a reduction in the use of oral corticosteroids were included in the economic analysis. The ICER would have been lower, as there would be QALY gains through an improvement in health-related quality of life. There was no comment on the effect on the ICER, but it is likely that it would lower the value.	The committee observed that the model structure incorporated long-term complications from steroid use. The modelling was accepted despite some effects of prolonged usage being irreversible (i.e. reduction in bone density), so there would be a minimal increase in benefit to the patient in reducing their dose. Conversely, some steroid-sparing benefits may not have been fully realised as they are reversible (i.e. weight gain and immunosuppression). Taking everything into account, the committee accepted that the model structure was appropriate for decision making	Limited data on the HRQoL associated with the reduction in use of oral corticosteroids
	Stopping rule for treatment	When treatment is stopped	Yes	The company included a stopping rule, but it was unclear if response was	The committee considered that treatment continuation based on an annual reassessment is	

				reassessed every year. There was no comment on the effect on the ICER, but it is likely that it would minimal.	appropriate for benralizumab because people have their asthma reassessed every year in clinical practice and this was consistent with NICE's guidance on reslizumab and mepolizumab.	
*Was the ICER sensitive to changes in this outcome? How did changes in the outcome affect the ICER (increase or decrease)? Abbreviations: ERG; Evidence Review group, HRQoL; health-related quality of life, ICER; incremental cost-effectiveness ratio, NICE; National Institute for Health and Care Excellence, QALY; quality-adjusted life-year, SoC; standard of care, TA; technology appraisal						

B.2.2 Resource use assumptions

The preferred assumptions about resource use and the associated costs are taken from National Institute for Health and Care Excellence (NICE) documents. This included the resource impact report and template in NICE technology appraisal (TA) 479 for reslizumab. The following assumptions apply.

The net price of reslizumab is commercial in confidence, so for this submission the list price will be used. The list price is £499.99 per 100 mg vial and £124.99 per 25 mg vial.[29]

Any patients with uncontrolled severe eosinophilic asthma are currently treated with inhaled corticosteroids and will continue to receive this therapy in addition to reslizumab if prescribed.[2] No costs were included in the resource impact template for other drugs. It is assumed that people will continue to receive that therapy regardless of whether they are prescribed reslizumab as an add-on therapy.[29]

The mean weight of 78 kg for the UK adult population will be used to calculate drug costs for reslizumab using the vial-based dosing from the summary of product characteristics.[30] The weight estimate is stated in the resource impact template for reslizumab.[29]

At the time of the appraisal for reslizumab, mepolizumab was not included in the scoping document. However, the committee considered that in practice both mepolizumab and reslizumab would have overlap in the recommended populations and the medicines could be used interchangeably.[29] The recommendations included criteria for stopping treatment, but there was no data to indicate how likely this was to occur and how many people might stop treatment. The template assumed that everyone has a full year of treatment and as a result the costs in the template might be slightly overstated.[29]

Mepolizumab and reslizumab both require 4-weekly dosing schedules. The analysis would equate this to a patient receiving 13 doses within a calendar year. The dosing of benralizumab is every 4 weeks for the first three doses, then every 8 weeks, resulting in a patient receiving eight doses within a calendar year.

The net price of benralizumab is commercial in confidence, so for this submission the list price will be used. The list price is £1,995 per 30 mg pre-filled syringe.[31]

TA565 compared benralizumab with the 100 mg mepolizumab powder for solution for injection. The Final Appraisal Determination states that the committee considered benralizumab to have similar efficacy to mepolizumab, although it acknowledged that there is some benefit for benralizumab, particularly in the method and frequency of administration.[31]

The benefit in the method of administration is no longer relevant, as mepolizumab is now available in the same pre-filled formulations as benralizumab. Therefore, the administration costs per dose of mepolizumab and benralizumab will be equivalent for the cost comparisons.

B.3 Clinical effectiveness

B.3.1 Identification and selection of relevant studies

A comprehensive search strategy was conducted to retrieve relevant clinical data from the published literature as part of the respective single technology appraisals (TAs) for mepolizumab (TA431[1]), reslizumab (TA479[2]) and benralizumab (TA565[3]). The searches for these submissions were comprehensive, evaluating the efficacy, health-related quality of life and safety of each treatment relative to other maintenance treatments for severe asthma.

The findings from the original search for mepolizumab have been applied herein and a further literature search to identify any additional studies has been completed. This further search was conducted on 14 January 2020, with the search date being effective from July 2015, which was the earliest completion date for the previous searches.

For inclusion in this submission, appropriate studies were defined as randomised, controlled trials comparing mepolizumab, reslizumab or benralizumab, either directly or versus placebo, in patients aged ≥12 years with severe (or refractory/difficult-to-treat/persistent/treatment-resistant/uncontrolled) asthma and reporting appropriate efficacy outcomes (exacerbations, lung function, asthma control, symptoms, hospitalisations).

During the most recent search, 484 citations were identified. The results were manually reviewed for relevance to this submission, with abstracts accessed if the publication title was unclear. No new studies were identified as being relevant to include; the majority of results related to other products, e.g. oral corticosteroids (OCS) or omalizumab, were review publications including no new data, or were subgroup analyses of the studies already detailed herein.

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to mepolizumab.

B.3.2 List of relevant clinical effectiveness evidence

This submission will consider both benralizumab and reslizumab as comparators to mepolizumab. Ideally, the main comparator would have been benralizumab as the aim of this review is to have the same population for benralizumab and mepolizumab. However, there was a lack of robust data presented for benralizumab in TA565 in patients with ≥400 eosinophils and three or more exacerbations to demonstrate similar efficacy with reslizumab, and hence it was felt that additional efficacy comparisons and a cost-minimisation analysis were needed against reslizumab in this subgroup of patients.

B.3.2.1 Mepolizumab

Details of four relevant, randomised, controlled, clinical trials have been included in this submission for mepolizumab: MEA112997 (DREAM),[20] MEA115588 (MENSA),[8] MEA115575 (SIRIUS),[32] and MUSCA.[33] All of these studies were international,

multicentre, randomised, double-blind, placebo-controlled studies including patients aged ≥12–82 years with a history of ≥2 exacerbations requiring treatment with systemic corticosteroids. The MEA115575 (SIRIUS) study required patients to have been treated with maintenance systemic corticosteroids for 6 months, and a stable OCS for at least 4 weeks prior to the first visit. The MUSCA study required patients to have been treated with regular high-dose inhaled corticosteroids (ICS) in the 12 months before screening, plus additional controller medication(s) for at least 3 months before screening. The MEA115588 (MENSA) study also used a double-dummy blinding approach. In MEA112997 (DREAM)[20] and MEA115588 (MENSA),[8] the primary efficacy endpoint was clinically significant asthma exacerbations, defined as worsening of asthma that required use of systemic corticosteroids and/or hospitalisation and/or emergency department (ED) visits. The MEA115575 (SIRIUS)[32] study was designed to assess the glucocorticoid-sparing effect of mepolizumab and as such the primary endpoint was reduction of OCS, defined as proportional reduction (%) of OCS dose during weeks 20–24 compared with the baseline dose, while maintaining asthma control. In the MUSCA study, the primary efficacy endpoint was the mean change from baseline in St George's Respiratory Questionnaire (SGRQ) total score at week 24. Secondary endpoints (all measured at week 24) were the mean change from baseline in pre-bronchodilator forced expiratory volume in 1 second (FEV_1), the proportion of SGRQ total score responders (i.e. patients achieving a ≥4-point reduction from baseline in SGRQ score) and the mean change from baseline in Asthma Control Questionnaire (ACQ)-5 score. The MEA115575 (SIRIUS)[32] study and the MEA112997 (DREAM) study were not included in the indirect treatment comparison analysis because of the different design and endpoints. However, both studies have been included in this fast track appraisal submission due to the overall relevance of the reported data.

B.3.2.2 Reslizumab

Four relevant, randomised, controlled, clinical trials have been included in this submission for reslizumab: Study 3081,[34] Study 3082,[35] Study 3083[35] and Study 3084.[36] All were multicentre, randomised, double-blind, placebo-controlled studies, and Study 3082 and Study 3083 employed the same study design, conducted across different investigational sites. All of the studies included patients aged 12–75 years (Studies 3081, 3082 and 3083 included patients aged 12–75 years, while Study 3084 included patients aged 18–65 years) with inadequately controlled asthma, receiving at least medium-dose ICS (ACQ-7 score ≥1.5). The primary efficacy endpoint was change from baseline in FEV_1 (over 16 weeks) in Studies 3081 and 3084, and frequency of asthma exacerbations (over 52 weeks) in Studies 3082 and 3083.

B.3.2.3 Benralizumab

Two relevant, randomised, controlled, clinical trials have been included in this submission for benralizumab: SIROCCO[37] and CALIMA.[38] Both were multicentre, randomised, double-blind, placebo-controlled studies, conducted across different investigational sites. Both studies included patients aged 12–75 years with inadequately controlled asthma, receiving medium- to high-dose ICS plus a long-acting β-agonist (LABA) with ≥1 asthma exacerbations in the prior year. SIROCCO and CALIMA also required patients to have an ACQ-6 score of ≥1.5. The primary

efficacy endpoint was change from the annual asthma exacerbation rate over 48 weeks in SIROCCO and 56 weeks in CALIMA.

Further details for each of the included studies are provided in Table 4, Table 5 and Table 6.

Table 4 Clinical effectiveness evidence for mepolizumab

Study	MEA112997 (DREAM)[20]	MEA115588 (MENSA)[8]	MEA115575 (SIRIUS)[32]	MUSCA[33]
Study design	International, multicentre, randomised, double-blind, placebo-controlled	International, multicentre, randomised, double-blind, placebo-controlled, double-dummy	International, multicentre, randomised, double-blind, placebo-controlled	International, multicentre, randomised double-blind, parallel group, placebo-controlled
Population	Severe asthma patients aged 12–74 years with a history of ≥2 exacerbations requiring treatment with systemic corticosteroids in the previous year and who had one or more of the following: • A blood eosinophil level of >300 cells/μL • Sputum eosinophils >3% • FeNO >50 ppb • Prompt deterioration of asthma control following a 25% reduction in regular maintenance dose of ICS or OCS	Severe asthma patients aged 12–82 years with a history of ≥2 exacerbations requiring treatment with systemic corticosteroids in previous year, receiving high-dose ICS, and who had a blood eosinophil level of >300 cells/μL within the 12 months prior to visit 1 or eosinophil level of >150 cells/μL at visit 1	Severe asthma patients aged 16–74 years treated with high-dose ICS and receiving 5–35 mg prednisone, or its equivalent, for ≥6 months, and who had a blood eosinophil level of >300 cells/μL within the 12 months prior to visit 1 or eosinophil level of >150 cells/μL at visit 1	Severe asthma patients aged 12 years and over with a history of ≥2 exacerbations requiring treatment with systemic corticosteroids in previous year, despite treatment with regular high-dose ICS in the 12 months before screening, plus additional controller medication(s) for at least 3 months before screening Pre-bronchodilator FEV_1 of less than 80% predicted in those aged ≥18 years, or less than 90% predicted in those aged 12–17 years Blood eosinophil count of ≥300 cells/μL within the 12 months before screening or a blood eosinophil count of ≥150 cells/μL at screening
Intervention(s)	IV mepolizumab 750 mg IV mepolizumab 250 mg IV mepolizumab 75 mg	IV mepolizumab 75 mg SC mepolizumab 100 mg	SC mepolizumab 100 mg	SC mepolizumab 100 mg plus standard of care
Comparator(s)	IV placebo	IV and SC placebo	SC placebo	SC placebo
Indicate if trial supports application for marketing	Yes	Yes	Yes	No

Study	MEA112997 (DREAM)[20]	MEA115588 (MENSA)[8]	MEA115575 (SIRIUS)[32]	MUSCA[33]
authorisation (yes/no)				
Reported outcomes specified in the decision problem	• Rate of clinically significant exacerbations • Rate of exacerbations requiring admission • Visits to the emergency department • Blood and sputum eosinophil counts • Pre-bronchodilator FEV_1 • ACQ score	• Rate of clinically significant exacerbations • Blood eosinophil counts • Mean increase from baseline in FEV_1 before bronchodilation • ACQ-5 score	• Percentage reduction in daily OCS dose • Annualised rate of asthma exacerbations • Mean change from baseline in FEV_1 before and after bronchodilation • ACQ-5 score	• Mean change from baseline in FEV_1 before and after bronchodilation • Annual rate of exacerbations • ACQ-5 score
All other reported outcomes	• AQLQ score • Safety	• SGRQ score • Global response to therapy rating • Immunogenicity • Safety	• Proportion of patients who had a reduction of ≥50% in OCS dose • Proportion of patients who had a reduction in OCS dose to ≤5 mg/day • Proportion of patients who had total cessation of OCS • Median percentage reduction in OCS dose • SGRQ score • Immunogenicity • Safety	• SGRQ score • Safety
Abbreviations: ACQ; Asthma Control Questionnaire, AQLQ; Asthma Quality of Life Questionnaire, FeNO; fractional exhaled nitric oxide concentration, FEV_1; forced expiratory volume in 1 second, ICS; inhaled corticosteroids, IV; intravenous, OCS; oral corticosteroids, SC; subcutaneous, SGRQ; St George's Respiratory Questionnaire				

Table 5 Clinical effectiveness evidence for reslizumab

Study	Study 3081[34]	Study 3082[35]	Study 3083[35]	Study 3084[36]
Study design	International, multicentre, randomised, double-blind, placebo-controlled	International, multicentre, randomised, double-blind, placebo-controlled	International, multicentre, randomised, double-blind, placebo-controlled	Multicentre, randomised, double-blind, placebo-controlled
Population	Patients aged 12–75 years with: • inadequately controlled asthma receiving at least medium-dose ICS (ACQ-7 score ≥1.5) • FEV_1 reversibility ≥12% with short-acting β-agonist • elevated blood eosinophils (≥400 cells/μL) during screening	Patients aged 12–75 years with: • elevated blood eosinophils (≥400 cells/μL) during screening • inadequately controlled asthma receiving at least medium-dose ICS (ACQ-7 score ≥1.5) • ≥1 exacerbation requiring treatment with systemic corticosteroids in the previous year • FEV_1 reversibility ≥12% with salbutamol	Patients aged 12–75 years with: • elevated blood eosinophils (≥400 cells/μL) during screening • inadequately controlled asthma receiving at least medium-dose ICS (ACQ-7 score ≥1.5) • ≥1 exacerbation requiring treatment with systemic corticosteroids in the previous year • FEV_1 reversibility ≥12% with salbutamol	Patients aged 18–65 years with: • inadequately controlled asthma receiving at least medium-dose ICS (ACQ-7 score ≥1.5) • FEV_1 reversibility ≥12% with short-acting β-agonist
Intervention(s)	IV reslizumab 0.3 mg/kg IV reslizumab 3.0 mg/kg	IV reslizumab 3.0 mg/kg	IV reslizumab 3.0 mg/kg	IV reslizumab 3.0 mg/kg
Comparator(s)	IV placebo	IV placebo	IV placebo	IV placebo
Indicate if trial supports application for marketing authorisation (yes/no)	Yes	Yes	Yes	Yes
Reported outcomes specified in the decision problem	• Change from baseline in pre-bronchodilator FEV_1 (over 16 weeks) • Blood eosinophil count	• Frequency of asthma exacerbations (over 52 weeks)	• Frequency of asthma exacerbations (over 52 weeks)	• Change from baseline in pre-bronchodilator FEV_1 (over 16 weeks) • Blood eosinophil count

Study	Study 3081[34]	Study 3082[35]	Study 3083[35]	Study 3084[36]
	• ACQ, ACQ-6 and ACQ-5 scores	• Change from baseline in pre-bronchodilator FEV_1 (over 16 weeks) • Blood eosinophil count • Change in ACQ-7 scores	• Change from baseline in pre-bronchodilator FEV_1 (over 16 weeks) • Blood eosinophil count • Change in ACQ-7 scores	• ACQ-7 score
All other reported outcomes	• Pre-bronchodilator FVC • Pre-bronchodilator forced expiratory flow at 25–75% FVC • ASUI and AQLQ scores • Rescue short-acting β-agonist use • Immunogenicity • Safety	• Change in ASUI and AQLQ scores • Short-acting β-agonist use • Time to first exacerbation • Immunogenicity • Safety	• Change in ASUI and AQLQ scores • Short-acting β-agonist use • Time to first exacerbation • Immunogenicity • Safety	• Rescue short-acting β-agonist use • FVC • ACQ-6 [post-hoc] • Immunogenicity • Safety
Abbreviations: ACQ; Asthma Control Questionnaire, AQLQ; Asthma Quality of Life Questionnaire, ASUI; Asthma Symptom Utility Index, FEV_1; forced expiratory volume in 1 second, FVC; forced vital capacity, ICS; inhaled corticosteroids, IV; intravenous				

Table 6 Clinical effectiveness evidence for benralizumab

Study	SIROCCO[37]	CALIMA[38]
Study design	International, randomised, double-blind, parallel group, placebo-controlled	International, randomised, double-blind, parallel group, placebo-controlled
Population	Patients aged 12–75 years with uncontrolled asthma receiving high-dose ICS plus LABA with/without additional asthma controller(s) and having a history of ≥2 asthma exacerbations in prior year (prespecified blood eosinophil ≥300/μL and <300/μL [2:1])	Patients aged 12–75 years with uncontrolled asthma receiving medium- to high-dose ICS plus LABA with/without additional asthma controller(s) and having a history of ≥2 asthma exacerbations in the prior year (prespecified blood eosinophil ≥300/μL and <300/μL [2:1])
Intervention(s)	SC benralizumab 30 mg Q4W SC benralizumab 30 mg Q4W × 3, Q8W × 4 EU adolescents: SC benralizumab 30 mg Q4W × 3, Q8W × 4	SC benralizumab 30 mg Q4W SC benralizumab 30 mg Q4W × 3, Q8W × 5 EU adolescents: SC benralizumab 30 mg Q4W × 3, Q8W × 5
Comparator(s)	SC placebo Q4W EU adolescents: SC placebo Q4W × 3, Q8W × 4	SC placebo Q4W EU adolescents: SC placebo Q4W × 3, Q8W × 5
Indicate if trial supports application for marketing authorisation (yes/no)	Yes	Yes
Reported outcomes specified in the decision problem	• Annual asthma exacerbation rate • Pulmonary function • Asthma symptom score and other asthma control metrics (e.g. ACQ-6) • Exacerbations associated with emergency room visit or hospitalisation	• Annual asthma exacerbation rate • Pulmonary function • Asthma symptom score and other asthma control metrics (e.g. ACQ-6) • Exacerbations associated with emergency room visit or hospitalisation
All other reported outcomes	• QoL (AQLQ[S] +12, EQ-5D) • HCRU and productivity loss (WPAI + CIQ) • Safety	• QoL (AQLQ[S] +12, EQ-5D) • HCRU and productivity loss (WPAI + CIQ) • Safety

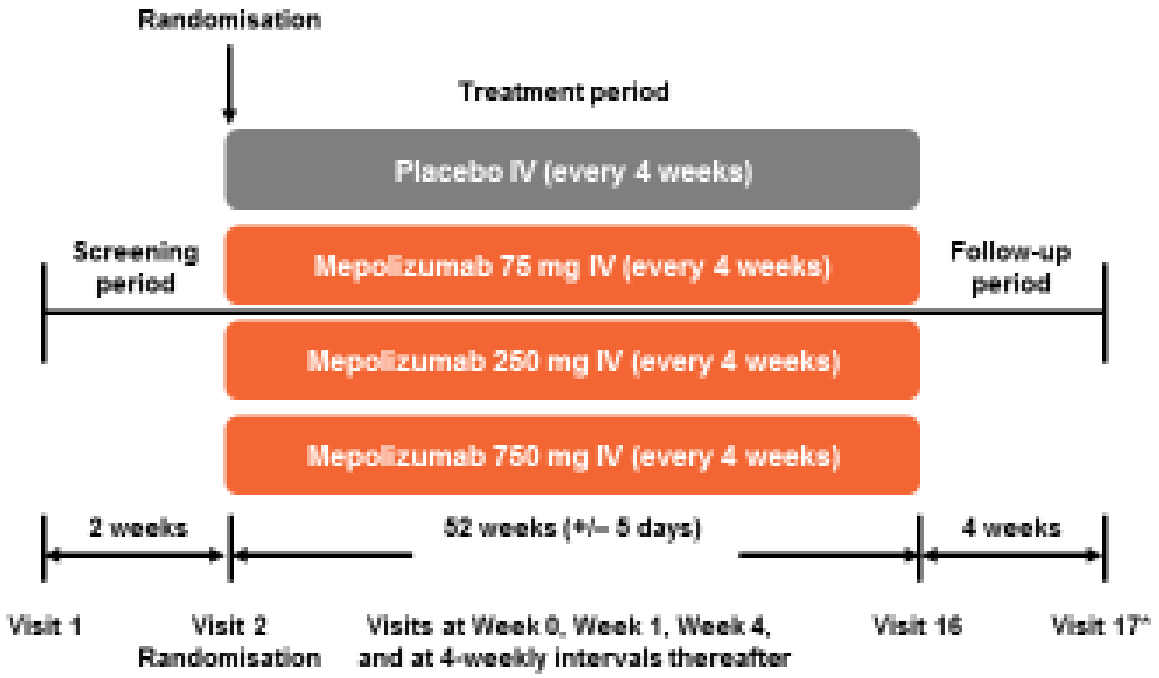
B.3.3 Summary of methodology of the relevant clinical effectiveness evidence

B.3.3.1 Mepolizumab MEA112997 (DREAM)[20]

B.3.3.1.1 MEA112997 (DREAM) trial design

MEA112997 (DREAM) was a multicentre, double-blind, placebo-controlled, parallel-group, 52-week dose-ranging study conducted at 95 investigational centres in 13 countries between 9 November 2009 and 5 December 2011 (see **Error! Not a valid bookmark self-reference.**). Patients were randomly assigned (in a 1:1:1:1 ratio) to receive one of three different doses (75 mg, 250 mg or 750 mg) of intravenous (IV) mepolizumab or matched placebo. Randomisation was stratified on the basis of whether the patient required daily treatment with OCS. A centralised computer-generated, permuted block schedule was used for randomisation purposes. Participants had to maintain their treatment (standard of care) throughout the study. The study aimed to randomise at least 151 subjects per group for 90% power to detect a decrease in exacerbation rate with increasing doses of mepolizumab.

Figure 2 MEA112997 (DREAM) trial design schematic



*Subjects were asked to return 16 weeks after study completion for a blood sample to test for the development of immunogenicity
Abbreviation: IV; intravenous

B.3.3.1.2 MEA112997 (DREAM) eligibility criteria

Participants were male or female and aged ≥12 years with a minimum weight of 45 kg, but in countries where local regulations or the regulatory status of study medication permitted enrolment of adults only, subjects were ≥18 years. Participants had severe refractory asthma in the previous year based on a history of two or more exacerbations requiring treatment with oral or systemic corticosteroids, despite the use of high-dose ICS and additional controller medication. Patients were also required to have need for additional maintenance treatments (e.g. long-acting β-agonist [LABA], leukotriene receptor antagonist [LTRA] or theophylline) in the 12 months prior to visit 1. The criteria also included subjects with persistent airflow obstruction as indicated by a pre-bronchodilator FEV_1 <80% predicted at visit 1 or visit 2, or peak flow diurnal variability of >20% on 3 or more days during the 2-week run-in period.

Additionally, subjects had evidence of eosinophilic inflammation as shown by one or more criteria at study entry or in the previous year:

- Sputum eosinophil count of 3% or more.
- Fractional exhaled nitric oxide concentration of 50 ppb or more.
- Asthma-related peripheral blood eosinophil count of 0.3 $\times 10^9$ per L or more.
- Prompt deterioration of asthma control after a 25% or less reduction in dose of regular maintenance ICS or OCS.

Patients met the American Thoracic Society criteria for a diagnosis of refractory asthma; all had stable treatment requirements of at least 880 µg fluticasone propionate (FP) equivalent per day (delivered dose), with or without maintenance OCS, and required additional controller drugs.

Exclusion criteria included current smokers or with a smoking history of >10 pack years (number of pack years = [number of cigarettes per day/20] × number of years smoked), parasitic infection in the 6 months before study entry, substantial uncontrolled comorbidity, possibility of pregnancy and history of poor treatment adherence.

B.3.3.1.3 MEA112997 (DREAM) settings and locations

The study was undertaken at 81 investigational sites in 13 countries: Argentina, Australia, Canada, Chile, France, Germany, South Korea, Poland, Romania, Russia, Ukraine, the UK and the USA. The first subject's first visit occurred on 9 November 2009 and the last subject's last visit occurred on 5 December 2011. There were a total of 33 subjects from the five centres within the UK, which represented 5% of the total intention-to-treat (ITT) population.

B.3.3.1.4 MEA112997 (DREAM) trial drugs and concomitant medications

Patients received 75 mg, 250 mg or 750 mg IV mepolizumab, or matched placebo (100 mL 0.9% sodium chloride [NaCl]). They received 13 infusions at 4-week intervals over a 52-week treatment period.

The study drugs were prepared by site staff who were aware of the study group assignments but were not involved in study assessments. Mepolizumab and placebo were identical in appearance and were administered by a staff member who was

unaware of the study group assignments. The blindness of those involved in the evaluation of the study was maintained at all times.

Additional asthma medications such as theophyllines or LTRAs were permitted provided they had been taken regularly in the 12 months prior to randomisation (visit 2, week 0). Maintenance OCS were permitted providing at least one of the exacerbations in the previous 12 months had occurred while the subject was receiving OCS and had been treated with a two-fold or greater increase in the dose of OCS.

The following medications were not allowed prior to the screening visit and throughout the study (Table 7):

Table 7 Prohibited medications (DREAM)

Medication	**Washout time prior to screening visits**
Investigational drugs	1 month (or 5 half-lives)
Corticosteroids intra-articular, short-acting intramuscular	1 month
Corticosteroids intramuscular, long-acting depot	3 months
Experimental anti-inflammatory drugs (non-biologics)	3 months
Methotrexate, troleandomycin, oral gold, cyclosporine, azathioprine	3 months
Omalizumab (Xolair®) or other biologicals for the treatment of inflammatory conditions	130 days
Chemotherapy/radiotherapy	12 months
Regular OCS or systemic corticosteroids for the treatment of conditions other than asthma	12 months
Abbreviation: OCS; oral corticosteroids	

B.3.3.1.5 MEA112997 (DREAM) outcomes specified in the scope

Outcomes included the rate of clinically significant exacerbations (primary endpoint), the rate of exacerbations requiring hospital admission, the frequency of visits to the ED, and blood and sputum eosinophil counts. All outcomes were prespecified in the study protocol.

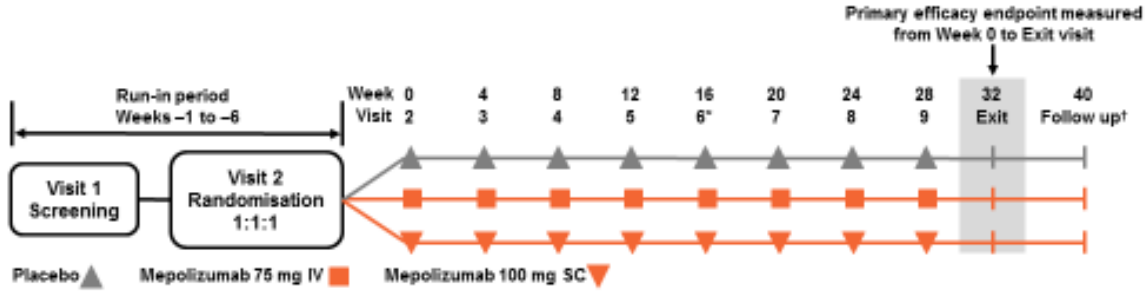
B.3.3.2 Mepolizumab MEA115588 (MENSA)[8]

B.3.3.2.1 MEA115588 (MENSA) trial design

MEA115588 (MENSA) was a double-blind, double-dummy, placebo-controlled, parallel-group, 32-week study evaluating the effects of mepolizumab 75 mg IV and 100 mg subcutaneous (SC) adjunctive therapy in subjects with severe refractory eosinophilic asthma (see **Error! Not a valid bookmark self-reference.**). Patients

were randomly assigned to receive either 75 mg IV or 100 mg SC mepolizumab or matched placebo in a 1:1:1 ratio. Randomisation was performed with the use of a centralised computer-generated, permuted-block schedule. The study aimed to randomise at least 180 subjects per group.

Figure 3 MEA115588 (MENSA) trial design schematic



*Subjects in a subset of countries returned 3–10 days post-visit 6 to obtain a PK sample
†Only subjects not entering the open-label extension study completed the follow-up visit
Abbreviations: IV; intravenous, PK; pharmacokinetic, SC; subcutaneous

B.3.3.2.2 MEA115588 (MENSA) eligibility criteria

The inclusion criteria were the same as MEA112997 (DREAM; subjects with severe asthma and a history of two or more exacerbations in the previous 12 months), except airway inflammation had to be characterised as eosinophilic in nature by one of the following:

- Elevated peripheral blood eosinophil count of ≥300 cells/μL demonstrated in the past 12 months prior to screening.
- Elevated peripheral blood eosinophil count of ≥150 cells/μL at screening.

B.3.3.2.3 MEA115588 (MENSA) settings and locations

The study was undertaken at 119 secondary care centres in 16 countries randomised and treated subjects: 18 in the USA and Japan, 11 in the Republic of Korea, ten in Canada and Germany, eight in France and Italy, seven in Argentina, five in Spain and Ukraine, four in Belgium, the Russian Federation and the UK, three centres in Australia and Chile, and one in Mexico. The study was initiated on 8 October 2012 (first subject screened) and was completed on 18 January 2014 (last subject's last visit). There were a total of 17 subjects from the four centres within the UK, which represented 5% of the total ITT population.

B.3.3.2.4 MEA115588 (MENSA) trial drugs and concomitant medications

Patients received 75 mg IV or 100 mg SC mepolizumab, or matched placebo (100 mL IV or equivalent volume SC 0.9% NaCl) at 4-week intervals over a 32-week treatment period.

The study drugs were prepared by site staff who were aware of the study group assignments but were not involved in study assessments. Mepolizumab and placebo were identical in appearance and were administered by a staff member who was unaware of the study group assignments. The blindness of those involved in the evaluation of the study was maintained at all times.

Additional asthma medications such as theophyllines or LTRAs were permitted provided they had been taken regularly in the 3 months prior to randomisation (visit 2, week 0). Maintenance OCS were permitted. Continuous positive airway pressure (CPAP) for the treatment of obstructive sleep apnoea was permitted, if initiated prior to the screening visit.

The following medications were not allowed prior to the screening visit and throughout the study (Table 8):

Table 8 Prohibited medications (MENSA and SIRIUS)

Medication	**Washout time prior to screening visit**
Investigational drugs	1 month or 5 half-lives, whichever is longer
Omalizumab (Xolair®)	130 days
Other monoclonal antibodies	5 half-lives
Experimental anti-inflammatory drugs (non-biological)	3 months
Immunosuppressive medications such as those listed below (not all inclusive)	
Corticosteroids intramuscular, long-acting depot if used to treat a condition other than asthma	3 months
Methotrexate, troleandomycin, cyclosporine, azathioprine	1 month
Oral gold	3 months
Chemotherapy used for conditions other than asthma	12 months
Regular systemic (oral or parenteral) corticosteroids for the treatment of conditions other than asthma	3 months

B.3.3.2.5 MEA115588 (MENSA) outcomes specified in the scope

Outcomes included the rate of clinically significant exacerbations (primary endpoint) and blood eosinophil counts. All outcomes were prespecified in the study protocol.

B.3.3.3 Mepolizumab MEA115575 (SIRIUS)[32]

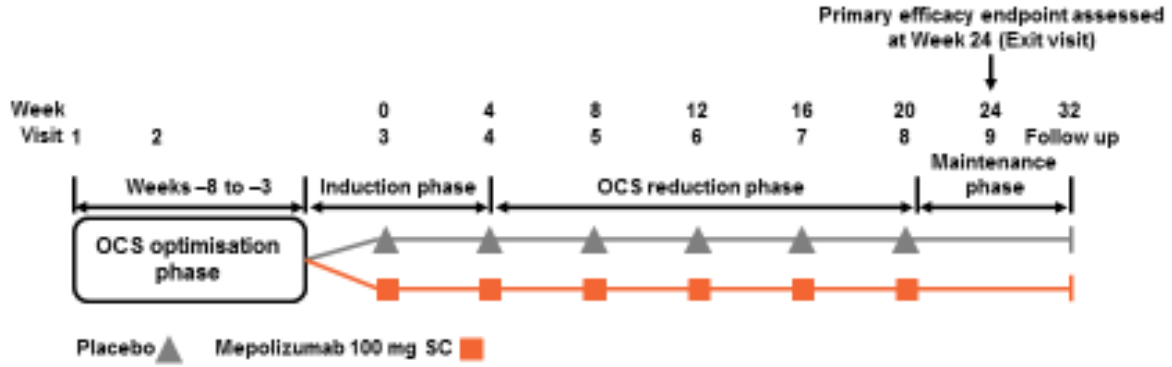
B.3.3.3.1 MEA115575 (SIRIUS) trial design

MEA115575 (SIRIUS) was a double-blind, placebo-controlled, parallel-group, 24-week study with four phases: 1) OCS optimisation, 2) Induction, 3) OCS reduction and 4) Maintenance (see **Error! Not a valid bookmark self-reference.**). The OCS optimisation phase was a run-in phase intended to ensure that patients entered the double-blind treatment phase on the lowest dose of prednisolone that would maintain asthma control. Patient's asthma status was assessed weekly; the lowest effective prednisolone dose was defined as the dose the patient was taking prior to the emergence of asthma symptoms or the occurrence of an exacerbation. The Induction phase was designed to allow for sufficient time for those patients randomised to the mepolizumab arm to achieve a decrease in eosinophilic inflammation prior to the reduction in prednisolone. During the OCS reduction phase, patients received four additional doses of double-blind study treatment. Patients were assessed for prednisolone reduction every 4 weeks. Prednisolone dose

titrations in the OCS optimisation and OCS reduction phases followed prespecified algorithms. Patients were maintained during the last 4 weeks of the study without any further prednisolone dose adjustment (i.e. Maintenance phase).

Patients were randomly assigned to receive either 100 mg SC mepolizumab or matched placebo in a 1:1 ratio. The study aimed to randomise at least 60 subjects per group.

Figure 4 MEA115575 (SIRIUS) trial design schematic



OCS dose titration occurred throughout the optimisation and reduction phases of the study. OCS titration did not necessarily coincide with the visits scheduled for mepolizumab administration as indicated above
Abbreviations: OCS; oral corticosteroids, SC; subcutaneous

B.3.3.3.2 MEA115575 (SIRIUS) eligibility criteria

Patients aged ≥12 years with severe eosinophilic asthma, a pre-bronchodilator FEV_1 <80% predicted, and a documented requirement for regular treatment with maintenance systemic corticosteroids (5.0–35 mg/day prednisolone or equivalent) and high-dose ICS (≥880 mcg/day [ex-actuator] FP or equivalent) were eligible. At the end of the run-in period, patients were eligible to be randomised if they had achieved a stable dose of OCS during the OCS optimisation phase.

Airway inflammation was characterised as eosinophilic in nature by one of the following:

- Elevated peripheral blood eosinophil count of ≥300 cells/μL demonstrated in the past 12 months prior to screening.
- Elevated peripheral blood eosinophil count of ≥150 cells/μL during the OCS optimisation phase.

B.3.3.3.3 MEA115575 (SIRIUS) settings and locations

The ITT population was comprised of subjects from 47 investigational sites in ten countries: eight in Germany, five in the Czech Republic, France and the USA, four in the UK, three in Australia and Canada, two in the Netherlands and Poland, and one in Mexico. There were a total of ten subjects from the four centres within the UK, which represented 7% of the total ITT population.

B.3.3.3.4 MEA115575 (SIRIUS) trial drugs and concomitant medications

Patients received 100 mg SC mepolizumab, or matched placebo (equivalent volume of 0.9% NaCl) at 4-week intervals over a 24-week treatment period.

The study drugs were prepared by site staff who were aware of the study group assignments but were not involved in study assessments. Mepolizumab and placebo were identical in appearance and were administered by a staff member who was unaware of the study group assignments. The blindness of those involved in the evaluation of the study was maintained at all times.

Prednisolone use was captured on a daily basis by each subject through the use of a daily eDiary. Site designated staff reviewed information to determine if subjects were taking the prednisolone dose instructed by the protocol and followed up with the subject accordingly.

Maintenance OCS was required per study eligibility criteria. OCS dose adjustments that occurred during the study were recorded. Additional asthma medications such as theophylline or LTRAs were permitted provided they had been taken regularly in the 3 months prior to randomisation (visit 3). CPAP for the treatment of obstructive sleep apnoea was permitted, if initiated prior to visit 1 (screening visit).

Medications prohibited during the MEA115575 (SIRIUS) were the same as those in the MENSA trial and have been detailed in Table 8.

B.3.3.3.5 MEA115575 (SIRIUS) outcomes specified in the scope

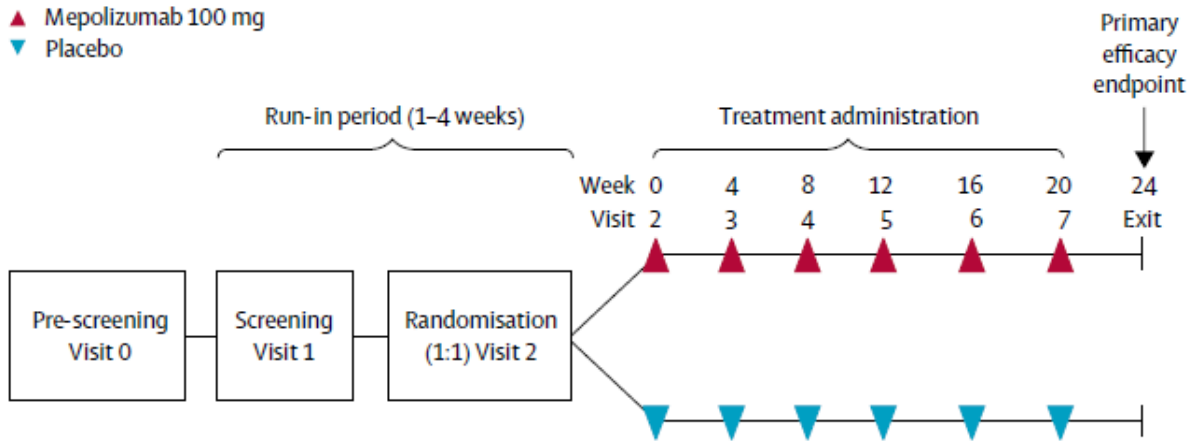
Outcomes included the percentage reduction in daily OCS dose, annualised rate of asthma exacerbations and the mean change from baseline in FEV_1 before and after bronchodilation. All outcomes were prespecified in the study protocol.

B.3.3.4 Mepolizumab (MUSCA)[33]

B.3.3.4.1 MUSCA trial design

MUSCA was a randomised, double-blind, placebo-controlled, parallel-group, multicentre, Phase 3b trial recruited in 146 hospitals or research centres in 19 countries. Patients who successfully completed the run-in period received either mepolizumab or placebo every 4 weeks for 24 weeks in addition to standard of care (**Error! Not a valid bookmark self-reference.**). The last dose was given at week 20. Spirometry measurements were taken at screening, baseline and every 4 weeks until week 24. Patients were randomly assigned (1:1) to receive a SC mepolizumab 100 mg or placebo using a centrally computer generated randomisation sequence using a permuted-block design of block size six, and the randomisation was done separately for each country.

Figure 5 MUSCA trial design schematic



B.3.3.4.2 MUSCA eligibility criteria

Eligible patients were 12 years or older with severe eosinophilic asthma who had experienced ≥2 exacerbations requiring treatment with systemic corticosteroids in the previous 12 months (for patients on maintenance OCS, two-fold or greater dose increases were required for inclusion), despite treatment with regular high-dose ICS in the 12 months before screening, plus additional controller medication(s) for ≥3 months before screening. Participants were required to have pre-bronchodilator FEV_1 of <80% predicted in adults, or <90% predicted in those aged 12–17 years, and blood eosinophil count of ≥300 cells/μL within the 12 months before screening, or a blood eosinophil count of ≥150 cells/μL at screening.

B.3.3.4.3 MUSCA settings and locations

MUSCA included participants from 146 hospitals or research centres in 19 countries (Argentina, Belgium, Bulgaria, Canada, Czech Republic, Estonia, France, Germany, Greece, Italy, Netherlands, Norway, Peru, Russia, Slovakia, Spain, Ukraine, UK and USA).

B.3.3.4.4 MUSCA trial drugs and concomitant medications

Patients received either SC mepolizumab or placebo. At each study centre, formulations of mepolizumab and placebo were prepared by staff members who were aware of study group assignments but were not involved in study assessments. Preparations were identical in appearance and administered in a masked manner.

Standard-of-care medications were permitted as part of the trial design. Patients who had received omalizumab within 130 days before screening were excluded.

B.3.3.4.5 MUSCA outcomes specified in the scope

Outcomes included mean change from baseline in pre-bronchodilator FEV1 and mean change from baseline in ACQ-5 score. Other patient-reported outcome

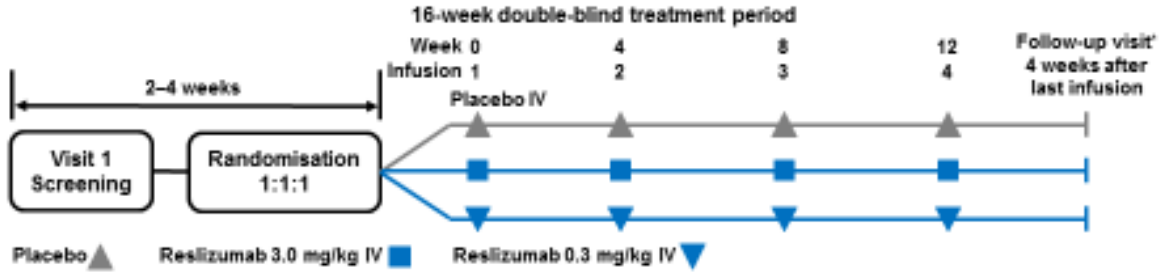
endpoints assessed at week 24 were proportion of ACQ-5 responders, daily asthma symptom scores, bronchodilator use and morning peak expiratory flow. All outcomes were prespecified in the study protocol.

B.3.3.5 Reslizumab Study 3081[34]

B.3.3.5.1 Study 3081 trial design

Study 3081 was an international, multicentre, double-blind, placebo-controlled, parallel-group, 16-week study conducted at 89 centres in 13 countries between February 2011 and September 2013 (Figure 6). The study consisted of a 2–4-week screening period and a 16-week, double-blind treatment period, with a final evaluation 4 weeks after the last infusion (end-of-treatment visit). Patients were randomly assigned (in a 1:1:1 ratio) to receive either 0.3 mg/kg or 3.0 mg/kg reslizumab infusion, or placebo. Randomisation was stratified based on age (12–17 years or ≥18 years) and history of asthma exacerbations within 12 months prior to screening (yes/no).

Figure 6 Study 3081 trial design schematic



*Only patients not entering the open-label extension study completed the follow-up visit
Abbreviation: IV; intravenous

B.3.3.5.2 Study 3081 eligibility criteria

Participants were male or female and aged 12–75 years with inadequately controlled asthma (ACQ-7 score ≥1.5) and airway reversibility (≥12% to short-acting β-agonist [SABA]), were receiving treatment with at least a medium-dose ICS (FP ≥440 µg/day or equivalent) and had at least one blood eosinophil count ≥400 cells/µL during the screening period.

Exclusion criteria included: other confounding lung disorders or pulmonary conditions; other clinically relevant comorbidities with potential to interfere with the study schedule, procedures or safety; hypereosinophilic syndrome; use of systemic corticosteroids 30 days prior to screening; current smoker (had smoked within last 6 months prior to screening); or use of systemic immunosuppressive or immunomodulating agents (e.g. anti-Immunoglobulin E [IgE] or anti-tumour necrosis factor (TNF) monoclonal antibodies, methotrexate, cyclosporine or interferon α) ≤6 months prior to screening.

B.3.3.5.3 Study 3081 settings and locations

The study was undertaken at 89 centres in 13 countries: Argentina, Belgium, Brazil, Canada, Colombia, France, Hungary, Israel, Mexico, the Netherlands, Poland, Sweden and the USA. No patients from the UK were recruited for this study.

B.3.3.5.4 Study 3081 trial drugs and concomitant medications

Patients received reslizumab 0.3 mg/kg, reslizumab 3.0 mg/kg or placebo, administered once every 4 weeks (total of four doses).

Patients were to refrain from using SABAs for 6 hours prior to each study visit (including screening). Patients taking LABAs were to withhold use for 12 hours prior to each study visit. Other permissible baseline medications included long-acting bronchodilators, leukotriene inhibitors or cromolyn. The dose of permitted baseline medications had to have been stable for 30 days prior to screening and expected to remain unchanged throughout the study.

B.3.3.5.5 Study 3081 outcomes specified in the scope

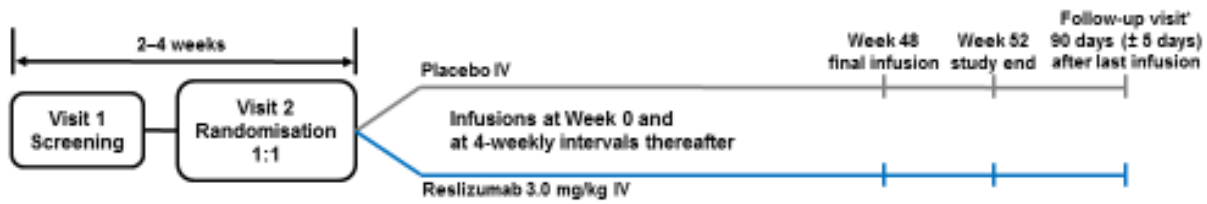
Outcomes included the change from baseline in pre-bronchodilator FEV_1 and blood eosinophil count. All outcomes were prespecified in the study protocol.

B.3.3.6 Reslizumab Study 3082 and Study 3083[35]

B.3.3.6.1 Study 3082 and Study 3083 trial design

Study 3082 and Study 3083 were duplicate international, multicentre, double-blind, placebo-controlled, parallel-group, 52-week studies conducted at 128 clinical research centres in Study 3082 and 104 centres in Study 3083, across Asia, Australia, North America, South America, South Africa, and Europe, between 12 April 2011 and 3 March 2014 (3082) and 22 March 2011 and 9 April 2014 (3083). The studies consisted of a 2–4-week screening period and a 52-week, double-blind treatment period, with a final evaluation 90 days after the last infusion (end-of-treatment visit) (Figure 7). Patients were randomly assigned (in a 1:1 ratio) to receive either 3.0 mg/kg reslizumab infusion or matching placebo. Randomisation was stratified by regular maintenance OCS use at enrolment and by region (USA vs outside of USA).

Figure 7 Study 3082 and 3083 trial design schematic



*Only patients not entering the open-label extension study completed the follow-up visit
Abbreviation: IV; intravenous

B.3.3.6.2 Study 3082 and Study 3083 eligibility criteria

Participants were male or female and aged 12–75 years with at least one blood eosinophil count of 400 cells per µL or higher during a 2–4-week screening period and inadequately controlled asthma (ACQ-7 score ≥1.5), who were receiving at least a medium dose of ICS (FP ≥440 µg per day, or equivalent) with or without another controller drug (including OCS). All patients had to have had at least one asthma exacerbation that needed oral, intramuscular or intravenous corticosteroid use within the past 12 months. As well as airway reversibility of ≥12% to β-agonist administration, demonstrated by withholding LABA therapy for ≥12 hours and SABA for ≥6 hours before measuring FEV_1, and then repeating the FEV_1 measurement after receiving SABA therapy (up to four puffs). If a patient's FEV_1 improved by ≥12% between the two tests, the patient was deemed as having airway reversibility. One retest was permitted during the screening period.

Exclusion criteria included: any clinically meaningful comorbidity that could interfere with the study schedule or procedures, or compromise safety; known hypereosinophilic syndrome; another confounding underlying lung disorder (e.g. chronic obstructive pulmonary disease, pulmonary fibrosis or lung cancer); current smoker (i.e. had smoked within the last 6 months prior to screening); prior use of an anti-human interleukin-5 (IL-5) monoclonal antibody (e.g. reslizumab, mepolizumab or benralizumab). Patients with pulmonary conditions with symptoms of asthma and blood eosinophilia (e.g. Churg-Strauss syndrome or allergic bronchopulmonary aspergillosis) or inadequately controlled, aggravating medical factors (e.g. rhinitis, gastro-oesophageal reflux disease or uncontrolled diabetes) were excluded. Patients who experienced an asthma exacerbation during the screening period were considered to have failed screening and were not randomised to study treatment.

B.3.3.6.3 Study 3082 and Study 3083 settings and locations

Study 3082 was undertaken at 104 centres in 17 countries: Australia, Belgium, Chile, Colombia, Czech Republic, Denmark, Hungary, Israel, Malaysia, New Zealand, Philippines, Poland, Russian Federation, South Africa, Sweden, Thailand and the USA. Study 3083 was undertaken at 128 centres in 15 countries: Argentina, Brazil, Canada, France, Germany, Greece, Republic of Korea, Mexico, Peru, Romania, Russian Federation, Slovakia, Taiwan, Ukraine and the USA. No patients from the UK were recruited for either study.

B.3.3.6.4 Study 3082 and Study 3083 trial drugs and concomitant medications

Patients received reslizumab 3.0 mg/kg or matching placebo administered once every 4 weeks, with the last dose given in week 48.

Patients were to refrain from using SABAs for 6 hours and withhold use of LABAs for 12 hours prior to each study visit that included spirometry or airway reversibility testing, including the screening visit. Patients continued their usual asthma treatment, including but not limited to LABAs, ICS, OCS (≤10 mg/day of prednisone or equivalent), leukotriene modifiers and cromolyn sodium, at constant doses. Treatments needed to be stable for 30 days before a patient was screened. Asthma drugs were reviewed monthly throughout the treatment period.

Concurrent use of any anti-human IL-5 monoclonal antibodies (e.g. reslizumab, mepolizumab or benralizumab) was prohibited. Patients were also prohibited from using omalizumab and all other biologic therapies within the 6-month period prior to screening. Other medication restrictions included: the use of any immunosuppressive or immunomodulatory agents (including, but not limited to, methotrexate, cyclosporine and interferon-α), or anti-TNF monoclonal antibodies within 6 months prior to screening; any live attenuated vaccines within 12 weeks prior to screening; and systemic corticosteroids (excluding OCS up to a maximum dose of 10 mg of prednisone daily or equivalent, if the dosage had been stable for 30 days prior to screening and continued without dosage changes throughout the study) and all other non-biologic investigational drugs within 30 days prior to screening.

B.3.3.6.5 Study 3082 and Study 3083 outcomes specified in the scope

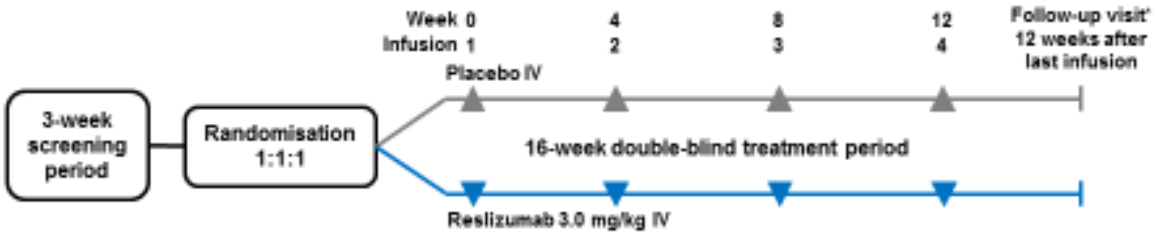
Outcomes included the frequency of asthma exacerbations, the recorded change in FEV_1 and blood eosinophil count. All outcomes were prespecified in the study protocol.

B.3.3.7 Reslizumab Study 3084[36]

B.3.3.7.1 Study 3084 trial design

Study 3084 was a multicentre, double-blind, placebo-controlled, parallel-group, 16-week study conducted at 66 centres across the USA between February 2012 and August 2013 (Figure 8). The study consisted of a 3-week screening period and a 16-week, double-blind treatment period, and a 12-week follow-up period. Patients were randomly assigned (in a 4:1 ratio) to receive either 3.0 mg/kg reslizumab infusion, or placebo. Randomisation was stratified based on history of asthma exacerbations within 12 months prior to screening (yes/no).

Figure 8 Study 3084 trial design schematic



*Only patients not entering the open-label extension study completed the follow-up visit.
Abbreviation: IV; intravenous

B.3.3.7.2 Study 3084 eligibility criteria

Participants were male or female and aged 18–65 years with asthma (ACQ-7 score ≥1.5) inadequately controlled by at least a medium-dose ICS at screening (FP ≥440 µg/day or equivalent). Patients were also required to demonstrate airway reversibility (≥12% to SABA) at screening.

Exclusion criteria included: underlying lung disorders or pulmonary conditions with symptoms of asthma and blood eosinophilia; other clinically relevant comorbidities with the potential to interfere with the study schedule, procedures or the safety of the

patient; known hypereosinophilic syndrome; current smoker (i.e. had smoked ≤6 months prior to screening); history of use of systemic immunosuppressive or immunomodulating therapy including anti-IgE or anti-TNF monoclonal antibodies or interferon-α ≤6 months prior to study entry; or the use of systemic corticosteroids within the 30 days prior to screening.

B.3.3.7.3 Study 3084 settings and locations

The study was undertaken at 66 centres across the USA only.

B.3.3.7.4 Study 3084 trial drugs and concomitant medications

Patients received reslizumab 3.0 mg/kg or placebo administered once every 4 weeks (total of four doses).

Patients were to refrain from using SABAs for 6 hours and LABAs for 12 hours before study visits. Other permitted baseline medications included LABAs, LTRAs, 5-lipoxengase inhibitors or cromolyn, provided the regimen was stable for 30 days before screening and not expected to change throughout the study; maintenance OCS were not allowed.

B.3.3.7.5 Study 3084 outcomes specified in the scope

Outcomes included the change from baseline in pre-bronchodilator FEV_1 and blood eosinophil count. All outcomes were prespecified in the study protocol.

A summary of these studies can be found below in Table 9.

Table 9 Comparative summary of trial methodology for mepolizumab studies

Trial number (acronym)	MEA112997 (DREAM)[20]	MEA115588 (MENSA)[8]	MEA115575 (SIRIUS)[32]	MUSCA[33]
Location	95 investigator sites 13 countries: Argentina, Australia, Canada, Chile, France, Germany, South Korea, Poland, Romania, Russian Federation, Ukraine, UK, USA	135 investigator sites 16 countries: Argentina, Australia, Belgium, Canada, Chile, France, Germany, Italy, Japan, Republic of Korea, Mexico, Russian Federation, Spain, Ukraine, UK, USA	47 investigator sites 10 countries: Australia, Canada, Czech Republic, France, Germany, Mexico, Netherlands, Poland, UK, USA	146 investigator sites 19 countries: Argentina, Belgium, Bulgaria, Canada, Czech Republic, Estonia, France, Germany, Greece, Italy, Netherlands, Norway, Peru, Russia, Slovakia, Spain, Ukraine, UK, USA
Trial design	A randomised, double-blind, placebo-controlled, parallel-group, dose-ranging trial	A randomised, double-blind, placebo-controlled, double-dummy, parallel-group trial	A randomised, double-blind, placebo-controlled, parallel-group trial	A randomised, double-blind, placebo-controlled parallel-group trial
Eligibility criteria for participants	Patients with severe asthma, aged ≥12 years with a requirement for regular treatment with high-dose ICS with or without maintenance OCS, in the previous 12 months. Patients were also required to have need for additional maintenance treatments (e.g. LABA, LTRA or theophylline) and evidence of eosinophilic airways inflammation. Eosinophilic airway inflammation could be demonstrated at screening, or documented in the previous 12 months,	The inclusion criteria were the same as the MEA112997 (DREAM) study, except airway inflammation had to be characterised as eosinophilic in nature by the following: • An elevated peripheral blood eosinophil count of ≥300 cells/μL demonstrated in the past 12 months prior to screening or an elevated peripheral blood eosinophil count of ≥150 cells/μL at screening	Patients with severe eosinophilic asthma aged ≥12 years, a pre-bronchodilator FEV_1 <80% predicted, and a documented requirement for regular treatment with maintenance systemic corticosteroids (5.0–35 mg/day prednisolone or equivalent) and high-dose ICS (≥880 mcg/day [ex-actuator] FP or equivalent) were eligible. At the end of the run-in period, patients were eligible to be randomised if they had achieved a stable dose of OCS during the OCS optimisation phase. Airway inflammation had to be characterised as eosinophilic	Patients with severe eosinophilic asthma ≥12 years, experiencing ≥2 exacerbations requiring treatment with systemic corticosteroids in the previous 12 months, despite treatment with regular high-dose corticosteroids and additional controller medications before screening, plus pre-bronchodilator FEV_1 of <80% (≥18 years) or <90% predicted (12–17 years) and a blood eosinophil count of ≥300 cells per μL within the 12 months before screening, or a blood eosinophil count of ≥150 cells/μL at screening

Trial number (acronym)	MEA112997 (DREAM)[20]	MEA115588 (MENSA)[8]	MEA115575 (SIRIUS)[32]	MUSCA[33]
	by one of the following characteristics: • An elevated peripheral blood eosinophil level of ≥300 cells/μL • Sputum eosinophils ≥3% • FeNO ≥50 ppb • Prompt deterioration of asthma control (based on documented clinical history or objective measures) following a ≤25% reduction in regular maintenance dose of inhaled or OCS dose in the previous 12 months Patients were further required to have a pre-bronchodilator FEV_1 <80% predicted and a history of two or more asthma exacerbations requiring treatment with systemic corticosteroids in the 12 months prior to visit 1, despite the use of high-dose ICS		in nature by one of the following: • An elevated peripheral blood eosinophil count of ≥300 cells/μL demonstrated in the past 12 months prior to screening • An elevated peripheral blood eosinophil count of ≥150 cells/μL during the OCS optimisation phase	
Trial drugs (the interventions for each group with sufficient details to allow replication, including how	Mepolizumab 75 mg IV (n=153) Mepolizumab 250 mg IV (n=152) Mepolizumab 750 mg IV (n=156)	Mepolizumab 75 mg IV + placebo SC (n=191) Mepolizumab 100 SC + placebo IV (n=194) Placebo SC and IV (n=191) Permitted medications were	Mepolizumab 100 mg SC (n=69) Placebo SC (n=66) Permitted medications: maintenance OCS was required per study eligibility	Mepolizumab 100 mg SC (n=274) Placebo SC (n=277) Permitted medications: standard of care Patients who had received

Trial number (acronym)	MEA112997 (DREAM)[20]	MEA115588 (MENSA)[8]	MEA115575 (SIRIUS)[32]	MUSCA[33]
and when they were administered) **Intervention(s) and comparator(s)** **Permitted and disallowed concomitant medication**	Placebo IV (n=155) Permitted medications: additional asthma medications such as theophyllines or LTRAs were permitted provided they had been taken regularly in the 3 months prior to randomisation (visit 2, week 0). Maintenance OCS was permitted CPAP for the treatment of obstructive sleep apnoea was permitted, if initiated prior to the screening visit Prohibited medications: refer to Table 7	the same as the MEA112997 (DREAM) study Prohibited medications: refer to Table 8	criteria. OCS dose adjustments that occurred during the study were recorded in the eCRF. Additional asthma medications such as theophylline or LTRA were permitted provided they had been taken regularly in the 3 months prior to randomisation (visit 3) CPAP for the treatment of obstructive sleep apnoea was permitted, if initiated prior to visit 1 (screening visit). At the end of the study (week 24), subjects who did not enter the OLE study were prescribed appropriate alternative asthma therapy if needed and as determined by the study investigator Prohibited medications: refer to Table 8	omalizumab within 130 days before screening were excluded from study
Primary outcomes (including scoring methods and timings of assessments)	**Clinically significant asthma exacerbations** Frequency of clinically significant exacerbations of asthma as defined by worsening of asthma that required use of oral/systemic corticosteroids and/or hospitalisation and/or ED visits. Use of systemic corticosteroids was defined	**Clinically significant asthma exacerbations** Frequency of clinically significant exacerbations of asthma as defined by worsening of asthma that required use of systemic corticosteroids and/or hospitalisation and/or ED visits. Use of systemic corticosteroids was defined as IV or oral steroid (e.g.	**Reduction of OCS** Proportional reduction (%) of OCS dose during weeks 20–24 compared with the baseline dose, while maintaining asthma control, categorised as follows: • 90–100% • 75–<90% • 50–<75% • >0–<50%	**Mean change in SGRQ total score from baseline to week 24** The SGRQ assesses symptoms, physical activity and the effect of the disease on the patient's life, using a 50-item questionnaire. The SGRQ is scored from 0–100, with higher scores indicating worse HRQoL; a 4-point reduction in score is

Trial number (acronym)	MEA112997 (DREAM)[20]	MEA115588 (MENSA)[8]	MEA115575 (SIRIUS)[32]	MUSCA[33]
	as IV or oral steroid (e.g. prednisolone) for at least 3 days or a single IM dose	prednisolone) for at least 3 days or a single IM dose	• No decrease in OCS, lack of control during weeks 20–24, or withdrawal from treatment	considered to be the minimal clinically important difference in interpreting a treatment benefit
Abbreviations: CPAP; continuous positive airway pressure, eCRF; electronic case report form, ED; emergency department, FeNO; fractional exhaled nitric oxide, FEV_1; forced expiratory volume in 1 second, HRQoL; health-related quality of life, ICS; inhaled corticosteroids, IM; intramuscular, IV; intravenous, LABA; long-acting β-agonist, LTRA; leukotriene receptor antagonist, OLE; open-label extension, OSC; oral corticosteroids, SC; subcutaneous, SGRQ; St George's Respiratory Questionnaire				

Table 10 Comparative summary of trial methodology for reslizumab studies

Trial number (acronym)	Study 3081[34]	Study 3082[35]	Study 3083[35]	Study 3084[36]
Location	• 89 investigator sites • 13 countries: Argentina, Belgium, Brazil, Canada, Colombia, France, Hungary, Israel, Mexico, Netherlands, Poland, Sweden, USA	• 128 investigator sites • 17 countries: Australia, Belgium, Chile, Colombia, Czech Republic, Denmark, Hungary, Israel, Malaysia, New Zealand, Philippines, Poland, Russian Federation, South Africa, Sweden, Thailand, USA	• 104 investigator sites • 15 countries: Argentina, Brazil, Canada, France, Germany, Greece, Republic of Korea, Mexico, Peru, Romania, Russian Federation, Slovakia, Taiwan, Ukraine, USA	• 66 investigator sites • USA
Trial design	International, multicentre, randomised, double-blind, placebo-controlled	International, multicentre, randomised, double-blind, placebo-controlled	International, multicentre, randomised, double-blind, placebo-controlled	Multicentre, randomised, double-blind, placebo-controlled
Eligibility criteria for participants	Participants were male or female and aged 12–75 years: • with inadequately controlled asthma (ACQ-7 score ≥1.5) • with airway reversibility (≥12% to SABA)	Participants were male or female and aged 12–75 years: • with at least one blood eosinophil count of 400 cells per µL or higher during a 2–4-week screening period	Participants were male or female and aged 12–75 years: • with at least one blood eosinophil count of 400 cells per µL or higher during a 2–4-week screening period	Participants were male or female and aged 18–65 years: • with asthma (ACQ-7 score ≥1.5) inadequately controlled by at least a medium-dose ICS at

Trial number (acronym)	Study 3081[34]	Study 3082[35]	Study 3083[35]	Study 3084[36]
	• who were receiving treatment with at least a medium-dose ICS (FP ≥440 µg/day or equivalent) • who had at least one blood eosinophil count ≥400 cells/µL during the screening period	• with inadequately controlled asthma (ACQ-7 score ≥1.5) • who were receiving at least a medium dose of ICS (FP ≥440 µg/day or equivalent) with or without another controller drug (including OCS) All patients had to have: • at least one asthma exacerbation that needed oral, intramuscular or intravenous corticosteroid use within the past 12 months • airway reversibility of ≥12% to β-agonist administration	• with inadequately controlled asthma (ACQ-7 score ≥1.5) • who were receiving at least a medium dose of ICS (FP ≥440 µg/day or equivalent) with or without another controller drug (including OCS) All patients had to have: • at least one asthma exacerbation that needed oral, intramuscular, or intravenous corticosteroid use within the past 12 months • airway reversibility of ≥12% to β-agonist administration	screening (FP ≥440 µg/day, or equivalent) • who demonstrated airway reversibility (≥12% to SABA) at screening
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])** **Permitted and disallowed**	Intervention: • Reslizumab 3.0 mg/kg, administered IV once every 4 weeks, for a total of 4 doses n=106 • Reslizumab 0.3 mg/kg, administered IV once every 4 weeks, for a total of 4 doses n=104 Comparator: • Placebo administered IV once every 4 weeks, for a	Intervention: • Reslizumab 3.0 mg/kg, administered IV once every 4 weeks, for a total of 13 doses n=245 Comparator: • Placebo administered IV once every 4 weeks, for a total of 13 doses n=244 Concomitant medications: • Permitted: 'usual asthma treatments, including…long-acting β	Intervention: • Reslizumab 3.0 mg/kg, administered IV once every 4 weeks, for a total of 13 doses n=232 Comparator: • Placebo administered IV once every 4 weeks, for a total of 13 doses n=232 Concomitant medications: • Permitted: 'usual asthma treatments, including…long-acting β	Intervention: • Reslizumab 3.0 mg/kg, administered IV once every 4 weeks, for a total of 4 doses n=398 Comparator: • Placebo administered IV once every 4 weeks, for a total of 4 doses n=98 Concomitant medications: • Permitted: long-acting bronchodilators, leukotriene modifiers, 5-

Trial number (acronym)	Study 3081[34]	Study 3082[35]	Study 3083[35]	Study 3084[36]
concomitant medication	total of 4 doses n=105 Concomitant medications: • Refrain from using SABAs for 6 hours prior to each study visit (including screening) • Withhold use of LABAs for 12 hours prior to each study visit • Other permissible baseline medications included long-acting bronchodilators, leukotriene inhibitors or cromolyn	agonists, ICS, OCS, leukotriene modifiers, cromolyn sodium' • Withhold SABA or LABA for 6 and 12 hours, respectively, prior to any study visit that included spirometry or airway reversibility testing (including screening). Disallowed: • Any anti-human IL-5 monoclonal antibodies (e.g. reslizumab, mepolizumab or benralizumab) • Omalizumab and all other biologic therapies within the 6-month period prior to screening • Immunosuppressive or immunomodulatory agents (including, but not limited to, methotrexate, cyclosporine and interferon-α), or anti-TNF monoclonal antibodies within 6 months prior to screening • Any live attenuated vaccines within 12 weeks prior to screening, and systemic corticosteroids (excluding OCS up to a maximum dose of 10 mg of prednisone daily or	agonists, ICS, OCS, leukotriene modifiers, cromolyn sodium' • Withhold SABA or LABA for 6 and 12 hours, respectively, prior to any study visit that included spirometry or airway reversibility testing (including screening) Disallowed: • Any anti-human IL-5 monoclonal antibodies (e.g. reslizumab, mepolizumab or benralizumab) • Omalizumab and all other biologic therapies within the 6-month period prior to screening • Immunosuppressive or immunomodulatory agents (including, but not limited to, methotrexate, cyclosporine and interferon-α), or anti-TNF monoclonal antibodies within 6 months prior to screening • Any live attenuated vaccines within 12 weeks prior to screening, and systemic corticosteroids (excluding OCS up to a maximum dose of 10 mg of prednisone daily or	lipoxygenase inhibitors, cromolyn • Withhold SABA or LABA for 6 and 12 hours, respectively, prior to any study visit that included spirometry or airway reversibility testing (including screening)

Trial number (acronym)	Study 3081[34]	Study 3082[35]	Study 3083[35]	Study 3084[36]
		equivalent, if the dosage had been stable for 30 days prior to screening and continued without dosage changes throughout the study) • All other non-biologic investigational drugs within 30 days prior to screening	equivalent, if the dosage had been stable for 30 days prior to screening and continued without dosage changes throughout the study) • All other non-biologic investigational drugs within 30 days prior to screening	
Primary outcomes (including scoring methods and timings of assessments)	Change from baseline in pre-bronchodilator FEV_1 (over 16 weeks)	Frequency of asthma exacerbations (over 52 weeks)	Frequency of asthma exacerbations (over 52 weeks)	Change from baseline in pre-bronchodilator FEV_1 (over 16 weeks)
Abbreviations: ACQ; Asthma Control Questionnaire, FEV_1; forced expiratory volume in 1 second, FP; fluticasone propionate, ICS; inhaled corticosteroids, IL-5; interleukin-5, IV; intravenous, LABA; long-acting β-agonist, OCS; oral corticosteroids, SABA; short-acting β-agonist, TNF; tumour necrosis factor				

Baseline characteristics including demographics and disease-related information are provided in Table 11.

Table 11 Characteristics of participants in the mepolizumab studies across treatment groups

Baseline characteristic	Mepolizumab 750 mg IV	Mepolizumab 250 mg IV	Mepolizumab 75 mg IV	Mepolizumab 100 mg SC	Placebo
MEA112997 (DREAM) (n=621)	n=156	n=152	n=153		n=155
Age, mean (SD)	48.6 (11.1)	49.4 (11.6)	50.2 (10.8)		46.4 (11.3)
Female, n (%)	93 (60)	93 (61)	104 (68)		97 (63)
Former smoker, n (%)	37 (24)	31 (20)	31 (20)		34 (22)
Duration of asthma, years (mean, SD)	19.1 (15.3)	20.4 (13.9)	19.0 (14.1)		17.9 (13.7)
Use of LABAs, n (%)	151 (97)	145 (95)	143 (93)		150 (97)
Maintenance OCS, n (%) Daily dose (mg; IQR)	47 (30) 13 (10–20)	50 (33) 10 (8–20)	46 (30) 10 (10–20)		45 (29) 10 (10–20)
Predicted pre-bronchodilator FEV_1, % (SD)	61 (16)	59 (17)	60 (16)		59 (15)
Blood eosinophil count ($\times 10^9$/L), mean (SD)	0.25 (0.93)	0.23 (1.20)	0.25 (0.95)		0.28 (1.01)
Severe exacerbations in previous year, mean (SD)	3.5 (2.8)	3.4 (2.4)	3.7 (3.1)		3.7 (3.8)
MEA115588 (MENSA) (n=576)			n=191	n=194	n=191
Age, mean (range)			50 (13–82)	51 (12–81)	49 (12–76)
Female, n (%)			106 (55)	116 (60)	107 (56)
Former smoker, n (%)			52 (27)	50 (26)	57 (30)
Duration of asthma, years (mean, SD)			19.8 (14.0)	20.5 (12.9)	19.5 (14.6)
Maintenance OCS, n (%) Daily dose (mg; IQR)			48 (25) 12 (1–40)	52 (27) 12.6 (2–50)	44 (23) 15.1 (5–80)

Predicted pre-bronchodilator FEV_1, % (95% CI)			61.4 (18.3)	59.3 (17.5)	62.4 (18.1)
Geometric mean blood eosinophil count on log_e scale (cells/µL)*			280 (±987)	290 (±1,050)	320 (±938)
Severe exacerbations in previous year, mean (SD)			3.5 (2.2)	3.8 (2.7)	3.6 (2.8)
MEA115575 (SIRIUS) (n=135)				n=69	n=66
Age, mean (range)				50 (16–74)	50 (28–70)
Female				44 (64)	30 (45)
Former smoker, n (%)				28 (41)	25 (38)
Duration of asthma, years (mean, SD)				17.4 (11.8)	20.1 (14.4)
Daily OCS, mg				12.5	15.0
Predicted pre-bronchodilator FEV_1, % (95% CI)				59.6 (17.0)	57.8 (18.5)
Geometric mean blood eosinophil count on log_e scale (cells/µL)*				250 (±1,245)	230 (±1,001)
Severe exacerbations in previous year, mean (SD)				3.3 (3.4)	2.9 (2.8)
MUSCA (n=551)				n=274	n=277
Age, mean				49.8	52.1
Female				149 (54)	176 (64)
Former smoker, n (%)				71 (26)	76 (27)
Duration of asthma, years (mean, SD)				19.5 (14.7)	19.6 (15.0)

Number of exacerbations in 12 months before screening, mean (SD)				2.9 (1.9)	2.7 (1.5)
Pre-bronchodilator FEV_1, L (mean, SD)				1.8 (0.6)	1.7 (0.6)
Geometric mean blood eosinophil count 10^9/L				0.30	0.35
*Values below LLOQ were replaced with a value that was 50% of the LLOQ. Abbreviations: CI; confidence interval, FEV_1; forced expiratory volume in 1 second, IQR; interquartile range, IV; intravenous, LABA; long-acting β-agonist, LLOQ; lower limit of quantification, OCS; oral corticosteroids, SC; subcutaneous, SD; standard deviation					

Table 12 Characteristics of participants in the reslizumab studies across treatment groups

Baseline characteristic	Reslizumab 0.3 mg/kg	Reslizumab 3.0 mg/kg	Placebo
Study 3082 (n=489)		n=245	n=244
Age, median (IQR)		48 (38–57)	49 (38–57)
Female, n (%)		142 (58)	161 (66)
Duration of asthma, years (mean, SD)		19.7 (15.2)	18.8 (14.2)
Use of LABAs, n (%)		214 (87)	207 (85)
Maintenance OCS, n (%)		46 (19)	46 (19)
Predicted pre-bronchodilator FEV_1, % (SD)		63.6 (18.6)	65.0 (19.8)
Blood eosinophil count (cells/µL), mean (SD)		696 (768)	624 (590)
Severe exacerbations in previous year, mean (SD)		1.9 (1.6)	2.1 (2.3)
Study 3083 (n=464)		n=232	n=232
Age, mean (SD)		48 (37–56.5)	48 (39.5–57)
Female , n (%)		144 (62)	150 (65)
Duration of asthma, years (mean, SD)		18.2 (14.4)	18.7 (13.3)
Use of LABAs, n (%)		190 (82)	192 (83)
Maintenance OCS, n (%)		27 (12)	27 (12)
Predicted pre-bronchodilator FEV_1, % (SD)		70.4 (21.0)	68.0 (18.9)
Blood eosinophil count (cells/µL), mean (SD)		610 (412)	688 (682)
Severe exacerbations in previous year, mean (SD)		1.9 (1.6)	2.0 (1.8)
Study 3081 (n=315)	n=104	n=106	n=105
Age, mean	44.5	43.0	44.2
Female, %	57	58	59

Baseline characteristic	Reslizumab 0.3 mg/kg	Reslizumab 3.0 mg/kg	Placebo
Duration of asthma, years	20.0	20.4	20.7
Use of LABAs, %	78	75	80
Total daily dose of ICS, mean, µg	756.3	813.5	756.7
Predicted pre-bronchodilator FEV_1, %	68.8	70.4	71.1
Blood eosinophil count (cells/mL), mean (range)	648 (100–3,700)	592 (100–2,300)	601 (100–3,700)
Exacerbations in previous year, %	56	57	54
Study 3084 (n=496)	NA	n=398	n=98
Age, mean	NA	44.9	45.1
Female, n (%)	NA	261 (66%)	54 (55%)
Duration of asthma, years	NA	26.2	25.8
Use of LABAs, n (%)	NA	307 (77)	80 (82)
Daily dose of ICS, mean, µg	NA	615.7	627.8
Predicted pre-bronchodilator FEV_1, %	NA	66.8	66.5
Blood eosinophil count (cells/µL), mean (range)	NA	281 (0–1,584)	277 (0–1,288)
Exacerbations in previous year, n (%)	NA	166 (42)	37 (38)
Abbreviations: FEV_1; forced expiratory volume in 1 second, ICS; inhaled corticosteroids, IQR; interquartile range, LABA; long-acting β-agonist, OCS; oral corticosteroids, SD; standard deviation			

B.3.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Details of the MEA112997 (DREAM), MEA115588 (MENSA), MEA115575 (SIRIUS) and MUSCA trial populations, hypothesis objective, statistical analysis, data management and subgroup analyses are summarised in Table 13 below.

Table 13 Statistical analysis and definition of study groups in the mepolizumab studies

Trial	Hypothesis	Sample size calculation	Statistical analysis	Subgroup analyses	Data management
MEA112997 (DREAM): superiority of mepolizumab vs placebo	Mepolizumab reduces the frequency of asthma exacerbations	A total of 151 randomised subjects per arm was estimated to give 90% power to detect a decrease in the exacerbation rate from 1.5 per year on placebo to 0.9 per year on mepolizumab (a 40% decrease) at the two-sided 5% significance level This assumed the number of exacerbations per year followed a negative binomial	**ITT population:** Consisted of all subjects who were randomised and received at least one dose of study medication. **Primary analysis:** The rate of clinically significant exacerbations over the 52-week treatment period was analysed using a negative binomial model with covariates of treatment group, baseline maintenance OCS therapy (OCS vs no OCS), region, exacerbations in the year prior to the study (as an ordinal variable) and baseline percent-predicted pre-bronchodilator FEV_1, with logarithm of time on treatment as an offset variable For the primary endpoint of exacerbations, for patients who withdrew, all data up to the time of patient withdrawal were included in the analyses. The primary analysis made a standard assumption known as MAR for missing data following withdrawal. This assumes that future exacerbations for those who withdrew could be predicted from their exacerbation history prior to withdrawal and from the exacerbation rate of similar patients on the same	Further subgroup analysis of the primary endpoint was performed to investigate the potential differential effects of mepolizumab according to each of the possible airway inflammation characteristics (recorded in the previous 12 months), i.e.: • Peripheral blood eosinophil level of ≥300 cells/μL that is related to asthma • Sputum eosinophils ≥3% • Exhaled nitric oxide ≥50 ppb (at visit 1 or visit 2) • Prompt deterioration of asthma control (based on documented clinical history or objective	For the primary endpoint of exacerbations, for patients who withdrew, all data up to the time of patient withdrawal were included in the analyses However, there are missing data for the period following withdrawal. The primary analysis made a standard assumption known as the MAR assumption. This assumes that future exacerbations for those who withdraw can be predicted from their exacerbation history prior to withdrawal and from the exacerbation rate of similar patients on the same treatment In order to understand how different assumptions regarding missing data could affect the results, two key sensitivity analyses were performed. In both of these sensitivity analyses, it is assumed that future exacerbations for patients

Trial	Hypothesis	Sample size calculation	Statistical analysis	Subgroup analyses	Data management
		distribution with a dispersion parameter k=0.7 and assumed that 15% of patients would withdraw from the study	treatment The rate of exacerbations requiring hospitalisation or ED visits was analysed as above for rate of clinically significant exacerbations. Analysis of FEV_1, ACQ scores and AQLQ scores were performed using mixed model repeated measures methods (including covariates as above plus baseline value), visit and interaction terms for visit by baseline, and visit by treatment group A closed testing procedure was used to ensure strong control of the type 1 error in adjusting for multiplicity across treatment comparisons and primary and secondary endpoints. Following an initial test for a linear trend of decrease in exacerbation rate with increasing dose of mepolizumab at a two-sided α=5% level, each dose of mepolizumab (75, 250 and 750 mg IV) was compared with placebo using a one-sided Hochberg testing procedure with a one-sided α=2.5%. A hierarchical 'gatekeeping' approach was used to control for multiplicity arising from the testing of the primary and secondary endpoints. A step-down testing procedure was applied where inference for an endpoint in the predefined hierarchy was dependent on statistical significance having been achieved for the previous endpoints in the hierarchy. For each endpoint, multiplicity across different treatment comparisons was controlled using the one-sided Hochberg testing procedure	measures) following a ≤25% reduction in regular maintenance dose of ICS or OCS dose For patients included in the sputum sub-study, subgroup analysis of the primary endpoint was performed according to whether their baseline sputum eosinophils were ≥3%	who withdrew from a mepolizumab arm could be predicted based on the exacerbation rate in the placebo arm, not on the mepolizumab arm. Both analyses showed similar results to the primary analysis

Trial	Hypothesis	Sample size calculation	Statistical analysis	Subgroup analyses	Data management
			Exploratory multivariate modelling was performed to investigate baseline variables predictive of overall number of exacerbations and of differential efficacy of mepolizumab. Baseline covariates included were age, sex, weight, baseline % predicted pre-bronchodilator FEV_1, number of exacerbations in the year prior to screening, region, baseline use of maintenance OCS, airway reversibility, blood eosinophil count and baseline total IgE concentration Consistency of treatment effect for covariates fitted in the primary efficacy endpoint analysis model were examined by fitting separate additional models to examine treatment effect according to each of the following subgroups: region, age, sex, baseline pre-bronchodilator % predicted FEV_1, exacerbations in the year prior to the study, race, baseline OCS therapy (OCS vs no OCS), reversibility at screening and baseline blood eosinophils		
MEA115588 (MENSA): superiority of mepolizumab vs placebo	Mepolizumab mitigates the requirement for frequent glucocorticoid use	A total of 180 subjects randomised to each treatment arm was estimated to have over 90% power to detect a 40% decrease in the exacerbation rate from 2.4	**ITT population:** Consisted of all subjects who were randomised and received at least one dose of trial medication **Interim analysis:** An IDMC ensured objective review of safety issues. The IDMC reviewed cardiovascular adverse events and all-cause mortality from MENSA and SIRIUS and from the open-label safety studies MEA115661 (COSMOS) and	Exploratory multivariate modelling was performed to investigate baseline variables predictive of overall number of exacerbations and of differential efficacy of mepolizumab. It was planned that if the mepolizumab IV and SC treatment groups	For the primary endpoint of exacerbations, for patients who withdrew, all data up to the time of patient withdrawal were included in the analyses However, there are missing data for the period following withdrawal. The primary analysis made a standard assumption known as the MAR assumption. This assumes that future

		p.a. on placebo to 1.44 p.a. on each of the mepolizumab treatment arms using a two-sided 5% significance level The calculation assumed the number of exacerbations per year followed a negative binomial distribution with a dispersion parameter k=0.8	MEA115666 (COLUMBA). The unblinded statistical analyses were performed by an independent SDAC at Duke University, NC. Unblinded results were not available to the study team. The SDAC communicated directly with the IDMC, and IDMC recommendations were made to a primary contact that was external to the mepolizumab study team at GSK There were no circumstances under which IDMC review of the data would lead to a recommendation to stop due to efficacy of mepolizumab. Therefore, no adjustment to the final alpha level for efficacy was made based on the safety stopping guidelines **Final analysis:** The rate of clinically significant exacerbations over the 52-week treatment period was analysed using a negative binomial model with covariates of treatment group, baseline maintenance OCS therapy (OCS vs no OCS), region, exacerbations in the year prior to the study (as an ordinal variable) and baseline percent-predicted pre-bronchodilator FEV_1, with logarithm of time on treatment as an offset variable For the primary endpoint of exacerbations, for patients who withdrew, all data up to the time of patient withdrawal were included in the analyses. Sensitivity analyses to investigate alternative assumptions regarding missing data were performed in the same way as described above for MEA112997 (DREAM)	produced similar results in the primary analysis then these treatment arms would be combined in this modelling analysis Baseline covariates considered for inclusion were age, sex, weight, baseline percent-predicted pre-bronchodilator FEV_1, number of exacerbations in the year prior to screening (i.e. 2, 3, 4+), region, baseline use of maintenance OCS, airway reversibility, blood eosinophil count and baseline total IgE concentration The rate of exacerbations was also tabulated by treatment group according to these covariates. For the multivariate modelling, age, baseline pre-bronchodilator percent-predicted FEV_1, reversibility at screening, blood eosinophils and total IgE concentration, were each treated as continuous. When	exacerbations for those who withdraw can be predicted from their exacerbation history prior to withdrawal and from the exacerbation rate of similar patients on the same treatment In order to understand how different assumptions regarding missing data could affect the results, two key sensitivity analyses were performed. In both of these sensitivity analyses, it is assumed that future exacerbations for patients who withdrew from a mepolizumab arm could be predicted based on the exacerbation rate in the placebo arm, not on the mepolizumab arm. Both analyses showed similar results to the primary analysis

			The rate of exacerbations requiring hospitalisation or ED visits and the rate of exacerbations requiring hospitalisation was analysed as above for rate of clinically significant exacerbations. Analysis of FEV_1 was performed using mixed model repeated measures methods (including covariates as above plus baseline value), visit and interaction terms for visit by baseline, and visit by treatment group. Analysis of SGRQ was performed using analysis of covariance with covariates as above plus baseline value A closed testing procedure was used to ensure strong control of the type 1 error in adjusting for multiplicity across treatment comparisons and primary and secondary endpoints. Each dose (75 mg IV and 100 mg SC) was compared with placebo using a one-sided Hochberg testing procedure with a one-sided α=2.5%. A hierarchical 'gatekeeping' approach was used to control for multiplicity arising from the testing of the primary and secondary endpoints. A step-down testing procedure was applied where inference for an endpoint in the predefined hierarchy was dependent on statistical significance having been achieved for the previous endpoints in the hierarchy. For each endpoint, multiplicity across different treatment comparisons was controlled using the one-sided Hochberg testing procedure	presenting tabulations, they were categorised as follows: age (12–17, 18–29, 30–49, 50–64, ≥65), percent-predicted FEV_1 (≤60%, >60–80%, >80%), baseline reversibility, blood eosinophils (<150, ≥150–<300, ≥300–<500, ≥500 cells/μL) and total IgE concentration (≤30, >30–≤700, >700 U/mL) Further tabulations of the primary endpoint were performed to investigate the potential differential effects of mepolizumab according to a) presence of nasal polyps at screening; b) previous failure on omalizumab (Xolair®) (assessed at screening) and c) the two possible protocol inclusion criteria for eosinophilic asthma, i.e. • Peripheral blood eosinophil level of ≥300 cells/μL in the previous 12 months prior to visit 1 that is related to asthma • Peripheral blood eosinophil level of ≥150 cells/μL at visit	

Trial	Hypothesis	Sample size calculation	Statistical analysis	Subgroup analyses	Data management
				1 that is related to asthma The relationship between these inclusion criteria and to what extent they intersect was also examined	
MEA115575 (SIRIUS): superiority of mepolizumab vs placebo	Mepolizumab (SC) reduces the use of maintenance oral glucocorticoids	The sample-size calculation was based on the proportional-odds model. It was estimated that with a sample of 120 patients, the study would have a power of 90% to detect an increase of 25% in the proportion of patients who had a reduction of 50% or more in the oral steroid dose, at a two-sided 5% significance level. On the assumption that such a reduction	**ITT population:** Consisted of all subjects who were randomised and received at least one dose of study medication **Interim analysis:** An IDMC was also used in SIRIUS to ensure external objective review of safety issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of data **Final analysis:** The primary efficacy endpoint was the percentage reduction of daily oral steroid dose during weeks 20–24 compared with the dose determined during the OCS optimisation phase, using the following categories: 1) 90–100%, 2) 75–<90% 3) 50–<75%, 4) >0–<50% and 5) no decrease in oral steroid dose, or lack of control during weeks 20–24 or withdrawal from treatment. Use of the categories enabled greater discrimination of response compared with analysis of proportions achieving a specific reduction, and the proportional odds model allowed for covariate adjustment. The primary endpoint was analysed	Further tabulations of the primary endpoint were performed to investigate the potential differential effects of mepolizumab according to: a) all covariates in the primary analysis model (for the subgroup analysis by OCS dose at baseline subjects will be grouped as follows: <10 mg, ≥10 mg–<15 mg, ≥15 mg–<25 mg, ≥25 mg prednisolone equivalent dose at baseline but analysed as a continuous variable) b) baseline blood eosinophils, with subjects grouped as follows: <150, ≥150–<300, ≥300–<500,	For the primary analysis of OCS reduction, all subjects in the ITT population were included. Subjects who withdrew early or who had missing data were assigned to the lowest efficacy category Sensitivity analysis was performed by assigning subjects to the efficacy category according to the reduction they had obtained by the time of their withdrawal (average dose in the 28 days prior to withdrawal). Subjects withdrawing within 28 days of an exacerbation were included in the lowest efficacy category. This analysis gave a similar result to the primary analysis

Trial	Hypothesis	Sample size calculation	Statistical analysis	Subgroup analyses	Data management
		would occur in 48% of the patients in the placebo group, the calculation implied that 73% of patients in the mepolizumab group would have this reduction. These proportions were associated with an odds ratio of 2.9 for a lower category of steroid use in the mepolizumab group than in the placebo group	using a proportional odds model for the above categories of oral steroid reduction, with covariates of region, number of years on oral steroids (<5 years vs ≥5 years) and baseline oral steroid dose For the primary analysis of OCS reduction, all subjects in the ITT population were included. Subjects who withdrew early or who had missing data were assigned to the lowest efficacy category Sensitivity analysis was performed by assigning subjects to the efficacy category according to the reduction they had obtained by the time of their withdrawal (average dose in the 28 days prior to withdrawal). Subjects withdrawing within 28 days of an exacerbation were included in the lowest efficacy category. This analysis gave a similar result to the primary analysis Analysis of the proportion of patients with specific reductions in the oral steroid dose was performed using a binary logistic regression model with adjustment for covariates. The median percentage reduction in dose was analysed with the use of the Wilcoxon test	≥500 cells/μ/L c) the two possible protocol inclusion criteria for eosinophilic asthma, i.e. • An elevated peripheral blood eosinophil level of ≥300 cells/μL that was related to asthma within the previous 12 months prior to visit 3 OR • Peripheral baseline eosinophil level ≥150 cells/μL between visit 1 and visit 3 that was related to asthma When carrying out the GSK-proposed population analyses, the same statistical analyses methods were used as the primary analyses	
MUSCA: superiority vs placebo as	Mepolizumab (SC) improved patient HRQoL	It was calculated that, with a sample size of 544	**ITT analysis** All randomly assigned patients who received at least one dose of trial	A non-predefined *post-hoc* analysis of the proportion of SGRQ and ACQ-5 responders	Patients with a missing score at week 24 were included in the least favourable category

Trial	Hypothesis	Sample size calculation	Statistical analysis	Subgroup analyses	Data management
add-on therapy		patients (272 per group), the study had a 98% probability of achieving a statistically significant between-group difference for SGRQ total score, assuming a true treatment difference of 6 points (SD 15.3). Additionally, this sample size had a 92% probability of achieving a difference of more than 4 points (MCID) between treatment groups	medication were included in the modified ITT population for efficacy assessments, with patients analysed according to their randomised treatment. A per-protocol analysis, including all patients in the modified ITT population who were not identified as full protocol deviators, was also planned for supplementary analysis of the primary endpoint. Safety assessments were done in the safety population, which consisted of all randomly assigned patients who received at least one dose of trial medication, analysed according to the actual treatment received for more than half of the administrations **Interim analysis** No interim data analyses were planned. **Final analysis** Data were analysed using mixed-effect model repeat measures adjusting for baseline values, region, baseline maintenance OCS therapy, exacerbations in the 12 months before the study, baseline percentage of predicted FEV_1 (excluding lung function endpoints), and interaction terms for visit by baseline and visit by treatment group as covariates. All data obtained up to and including week 24 were included in the model. Residuals were assessed to check model assumptions and no violations were noted Exacerbation rates were analysed using negative binomial regression with region,	by blood eosinophil count thresholds at baseline (≥150, ≥300 and ≥500 cells per μL) was performed	in the analysis

Trial	Hypothesis	Sample size calculation	Statistical analysis	Subgroup analyses	Data management
			baseline maintenance OCS therapy, exacerbations in the year before the study, and baseline percentage of predicted FEV_1 as covariates Univariate models were used to investigate the effect of baseline blood eosinophil count on the continuous primary and secondary outcomes at week 24 and clinically significant exacerbations, adjusting for the same covariates as used in the main analysis of the corresponding endpoint and an interaction between treatment and log baseline blood eosinophil count		

Abbreviations: ACQ; Asthma Control Questionnaire, AQLQ; Asthma Quality of Life Questionnaire, ED; emergency department, FEV_1; forced expiratory volume in 1 second, GSK; GlaxoSmithKline, HRQoL; health-related quality of life, ICS; inhaled corticosteroids, IDMC; Independent data monitoring committee, IgE; immunoglobulin E, ITT; intention-to-treat, IV; intravenous, MAR; missing at random, MCID; minimal clinically important difference, OCS; oral corticosteroids, SC; subcutaneous, SGRQ; St George's Respiratory Questionnaire

Table 14 Statistical analysis and definition of study groups in the reslizumab studies

Trial	Hypothesis	Sample size calculation	Statistical analysis	Subgroup analyses	Data management
Studies 3082 and 3083: superiority of reslizumab vs placebo	Reslizumab reduces exacerbations in patients with inadequately controlled asthma	A sample size of 460 patients (230 patients per group) was estimated to provide about 90% power (with a	**ITT population**: Consisted of all randomly assigned patients **Primary analysis**: The frequency of clinical asthma exacerbations (the primary endpoint) was analysed with a	Pooled data from both studies were used to do subgroup analyses for the frequency of clinical asthma exacerbations and change in FEV_1 outcomes	For efficacy analyses, assessments collected at the early withdrawal visit were considered as the next scheduled visit if they were performed at least 3, but no more than 5, weeks since the last study drug administration. All

Trial	Hypothesis	Sample size calculation	Statistical analysis	Subgroup analyses	Data management
		significance of 0.05) to detect a 33% reduction in the frequency of clinical asthma exacerbations by reslizumab compared with placebo. This estimate accounted for a maximum 10% false-positive rate for the blood eosinophil test at enrolment and a 9% dropout rate in both treatment groups	negative binomial regression model, including treatment group and randomisation stratification factors as model factors, and logarithm of follow-up time (excluding the summed duration of exacerbations in the treatment period) as an offset variable; sensitivity analysis without exclusion of summed durations was also done. RRs vs placebo (with 95% CIs) were estimated from the model and used likelihood-based χ^2 tests (two-sided, α=0.05) to test for between-group differences A prespecified, fixed-sequence multiple testing procedure was applied to the primary efficacy variable and eight secondary efficacy variables to control the type 1 error rate for multiple testing. If the two-sided p-value from the primary variable comparison was ≤0.05, the next comparison of interest (first secondary variable) was interpreted inferentially at 0.05. This process continued through the secondary variables until all comparisons of interest were interpreted inferentially, or until the two-sided p-value for a comparison was >0.05, at which point no further comparisons were interpreted inferentially.		available data were included for evaluation. Missing or invalid values were not imputed unless otherwise specified. A low (<5%) dropout rate was anticipated because all patients maintained their background therapies throughout the study; all efforts were made to treat and retain patients after clinical asthma exacerbations. The primary analysis model was unbiased if the missing data mechanism appeared to be random. As described above, a sensitivity analysis using imputation for missing data was performed to assess the robustness of the primary model Missing or invalid laboratory test results were not estimated for biomarker analysis and safety analysis

Trial	Hypothesis	Sample size calculation	Statistical analysis	Subgroup analyses	Data management
			Results of testing the frequency of clinical asthma exacerbations specifically requiring systemic corticosteroids could be interpreted inferentially at an alpha level of 0.05 provided that results of all tests for secondary variables were significant. Analyses of other and exploratory efficacy variables were not adjusted for multiple testing, and thus p-values are nominal. To assess the robustness of the primary analysis, two sensitivity analyses were performed: 1. Analysis using an offset variable that did not exclude the summed duration of clinical asthma exacerbations from the follow-up time 2. Analysis using a multiple imputation method for missing data to evaluate whether the primary analysis model was unbiased in terms of patterns of missing data (clinical asthma exacerbation and exposure data for patients who withdrew early were imputed)		
Study 3081: superiority of reslizumab	Reslizumab improves lung function, asthma control and quality of	300 patients (100 per group) provided at least 90% power at the	**FAS**: Consisted of all randomised patients who received at least one dose of study drug	Not defined	Missing data were not imputed in the primary mixed effect model for repeated measures analysis. The primary analysis was unbiased if the missing data

Trial	Hypothesis	Sample size calculation	Statistical analysis	Subgroup analyses	Data management
vs placebo	life	0.05 significance level to detect a difference in change from baseline in FEV_1 between a reslizumab dose (3.0 mg/kg or 0.3 mg/kg) and placebo, using a two-sided t-test and by mixed effect model for repeated measures simulation. This estimate assumed an equal effect size for both reslizumab doses	Pulmonary function tests were excluded from the FAS if they were obtained at scheduled visits that were preceded by usage (within 7 days) of a limited subset of medications that could significantly confound interpretation (including OCS or systemic corticosteroids, or the addition of a LABA or a long-acting muscarinic antagonist if not taken at baseline) and in violation of the protocol **Primary analysis**: Change from baseline in FEV_1 over 16 weeks was analysed using a mixed effect model for repeated measures with treatment, stratification factors, sex, visit, and treatment and visit interaction as fixed effects, height and baseline values as covariates, and patients as a random effect An unstructured covariance matrix was used for within-patient correlation modelling. In case there was a convergence problem with the unstructured covariance, a first order autoregressive covariance structure was assumed Treatment difference (and 95% CI) was estimated from the mixed effect model for repeated		mechanism was ignorable. As described, a sensitivity analysis using imputation for missing data was performed to assess the robustness of the primary analysis

Trial	Hypothesis	Sample size calculation	Statistical analysis	Subgroup analyses	Data management
			measures. Treatment effect was tested using a two-sided t-test at the 0.05 significance level A prespecified, hierarchical testing procedure was applied to the primary efficacy variable to control the type 1 error rate for the two comparisons of reslizumab vs placebo. Statistical significance was claimed in the order of reslizumab 3.0 mg/kg first and 0.3 mg/kg second Specifically, a treatment effect was considered significant for reslizumab 3.0 mg/kg if the p-value was ≤0.05. Significance was claimed for both reslizumab doses if the p-values were both ≤0.05. No significance was claimed otherwise The secondary analysis of the primary efficacy variable, and analyses of secondary efficacy variables, were not adjusted for multiple testing, and thus p-values are nominal To assess the robustness of the primary analysis, two sensitivity analyses were performed: 1. Analysis using all FEV_1 measurements without data exclusions for confounding medications		

Trial	Hypothesis	Sample size calculation	Statistical analysis	Subgroup analyses	Data management
			2. Analysis using a multiple imputation method for missing data (104) and excluding data for which concomitant medications could confound interpretation (i.e. using the FAS)		
Study 3084: superiority of reslizumab vs placebo	Reslizumab improves lung function and asthma control irrespective of baseline eosinophil count	Not defined	**FAS:** Consisted of all randomised patients who received at least one dose of study drug Results from patients using concomitant medication (including OCS or systemic corticosteroids or addition of an LABA or a long-acting antimuscarinic agent if not taken at baseline) within 7 days preceding a scheduled visit that could significantly confound interpretation of the efficacy parameters were excluded from the FAS. A blind data review meeting was conducted before the database lock to determine the exclusion of affected, individual pulmonary function tests **Primary analysis**: The primary endpoint was analysed using a linear regression model with model effects including treatment (reslizumab or placebo), blood eosinophils at baseline, and the	A secondary analysis was performed for the primary variable for patients included in the FEV_1 subpopulation (all patients in the FAS with percent-predicted FEV_1 <85% at baseline) using the same linear regression analysis as the primary endpoint Change in FEV_1 by discrete blood eosinophil thresholds was prespecified; a post hoc analysis of FEV_1, FVC and ACQ-7 stratified by eosinophil quartile categories was also performed. Secondary variables, including change in FEV_1 from baseline to planned time points, were analysed using a mixed effects model for repeated measures	

Trial	Hypothesis	Sample size calculation	Statistical analysis	Subgroup analyses	Data management
			interaction of treatment and eosinophils. The interaction was tested at the significance level 0.10 using the FAS		
Abbreviations: ACQ; Asthma Control Questionnaire, CI; confidence interval, FAS; full analysis set, FVC; forced vital capacity, ITT; intention-to-treat, LABA; long-acting β-agonist, OCS; oral corticosteroids, RR; relative risk					

Full details of the numbers of participants eligible to enter the abovementioned trials are included in Appendix E.

B.3.5 Quality assessment of the relevant clinical effectiveness evidence

B.3.5.1 Validity of the randomised, controlled trials results

The quality of each source of evidence provided in section B.3.2 has been appraised in order to assess the validity and robustness of the overall design and execution of the mepolizumab and reslizumab randomised, controlled trials.

B.3.5.2 Quality assessment methods

The principles detailed in the York Centre for Reviews and Dissemination guidance for undertaking reviews in healthcare[39] were applied to assess the quality and risk of bias of the randomised, controlled trials included in this submission. This guidance incorporates the criteria for assessment of risk of bias and generalisability suggested by the National Institute for Health and Care Excellence (NICE) (Full technology assessment template guide, section B.3.5.2).

All of the included mepolizumab and reslizumab randomised, placebo-controlled trials have been identified as providing robust evidence in supporting the requested change for mepolizumab.

B.3.5.3 Routine clinical practice in England

The British Guideline the Management of Asthma recommends that the following points are assessed for diagnosis:[10]

- Spirometry to assess bronchodilator reversibility.
- A history of recurrent episodes of symptoms.
- The patient's status with a validated symptom questionnaire, which includes ACQ.
- Lung function tests (FEV_1).
- Difficult asthma is defined as persistent symptoms and/or frequent asthma attacks despite treatment with high-dose ICS.
- Blood eosinophil analysis may be a useful predictor of future risk of asthma attacks in adults, and sputum eosinophil analysis to guide treatment can reduce asthma exacerbation rates in adults.

Change from baseline in pre-bronchodilator FEV_1 and the frequency of asthma exacerbations, which were primary efficacy endpoints used across the studies included herein, reflect current, recommended practice as noted above in the guidelines. Secondary endpoints included across the studies are also representative of the diagnosis and monitoring recommendations reported by the British national guideline.

B.3.5.4 Summary of results of the quality assessment of the mepolizumab and reslizumab randomised controlled trials

As can be seen in Table 15, the results indicate that all included studies are of good quality. All clinical trials were randomised, double-blind and reported prespecified outcomes. Study groups were similar within individual studies, there were no unexpected drop outs and most studies employed true ITT analyses.

Please refer to Appendix E for a complete quality assessment of each trial.

Table 15 Summary of quality assessment for the mepolizumab and reslizumab randomised, controlled trials

Study ID and publications	Mepolizumab				Benralizumab		Reslizumab			
	MEA112997 (DREAM)[20]	*MEA115588 (MENSA)*[8]	*MEA115575 (SIRIUS)*[32]	*MUSCA*[33]	*SIROCCO*[37]	*CALIMA*[38]	*Study 3081*[34]	*Study 3082*[35]	*Study 3083*[35]	*Study 3084*[36]
Was the randomisation method adequate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the allocation adequately concealed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the groups similar at study outset in terms of prognostic factors, e.g. severity of disease?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No	No	No	No	No	No	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No	No	No	No	No	No	No
Did the analysis include an ITT analysis?	Yes	Yes*	Yes	Yes	Yes	Yes	Yes*	Yes	Yes	Yes*
Did the authors of the study publication declare any conflicts of interest?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

B.3.6 Clinical effectiveness results of the relevant trials

The outcomes detailed below from across the included studies are those deemed relevant to the overall assessment, i.e. primary study endpoints and those applied as at least part of the indirect treatment comparison analysis that has been completed. The outcomes included are:

- asthma exacerbations
- eosinophil counts
- FEV_1
- ACQ score.

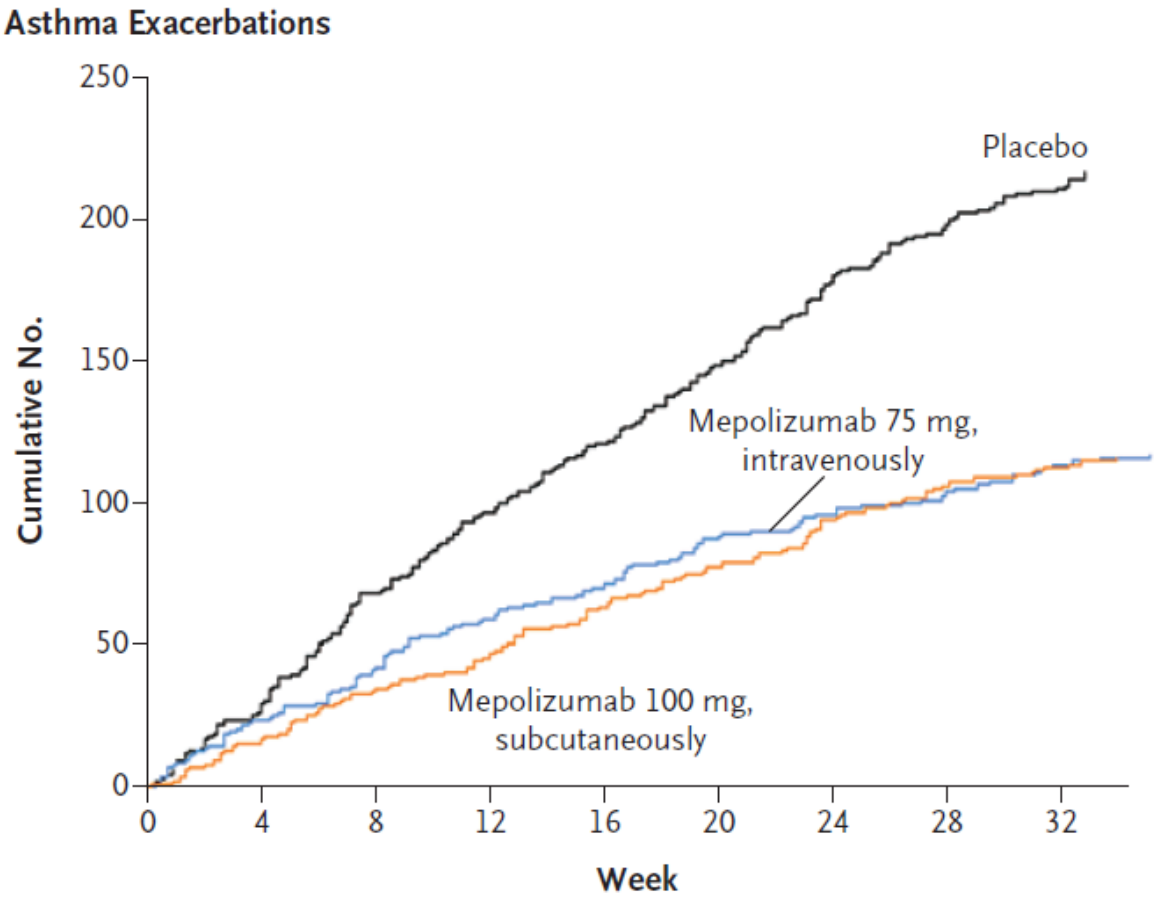
The SIRIUS trial and Studies 3082 and 3083 analysed the ITT population of all randomised patients. The DREAM and MENSA trials, and Studies 3081 and 3084 analysed the full analysis set (FAS) of patients who received at least one dose of the study drug.

B.3.6.1 Mepolizumab MEA115588 (MENSA): Primary efficacy outcome – frequency of clinically significant asthma exacerbations at week 32

All patients who received at least one dose of a study drug were included in a modified ITT analysis.[8] The primary outcome measure was annualised frequency of clinically significant exacerbations at week 32. Clinically significant exacerbations were defined as worsening of asthma such that the treating physician elected to administer systemic glucocorticoids for at least 3 days, or the patient visited an ED or was hospitalised.

Figure 9 and Table 16 show the rate of exacerbations was reduced by 47% (95% confidence interval [CI]: 28, 60) among patients receiving IV mepolizumab and by 53% (95% CI: 36, 65) among those receiving SC mepolizumab, as compared with those receiving placebo ($p<0.001$ for both comparisons). Exacerbations necessitating an ED visit or hospitalisation were 9% and 6% in the IV and SC mepolizumab groups, respectively, compared with 13% in the placebo group. The relative reduction in such events was 32% in the group receiving IV mepolizumab ($p=0.30$) and 61% in the group receiving SC mepolizumab ($p=0.02$).

Figure 9 Numbers of asthma exacerbations in patients receiving either IV or SC mepolizumab or placebo[8]



Abbreviations: IV; intravenous, SC; subcutaneous

Table 16 Summary of primary efficacy outcomes at week 32[8]

	Placebo group (n=191)	IV mepolizumab (n=191)	SC mepolizumab (n=194)
Mean rate of clinically significant exacerbations	1.74	0.93	0.83
Difference from placebo	–	47 (28, 60) p<0.001	53 (36, 65) p<0.001
Mean rate of exacerbations requiring hospitilisation or ED visit	0.20	0.14	0.08
Difference from placebo	–	32 (−41, 67) p=0.30	61 (17, 82) p=0.02
Mean rate of exacerbations requiring hospitalisation **Difference from placebo**	0.10 –	0.06 39 (−66, 77) p=0.33	0.03 69 (9, 89) p=0.03

Data in parentheses are 95% CIs. 'Difference from placebo' is the percent reduction as compared with the placebo group. Abbreviations: CI; confidence interval, ED; emergency department, IV; intravenous, SC; subcutaneous

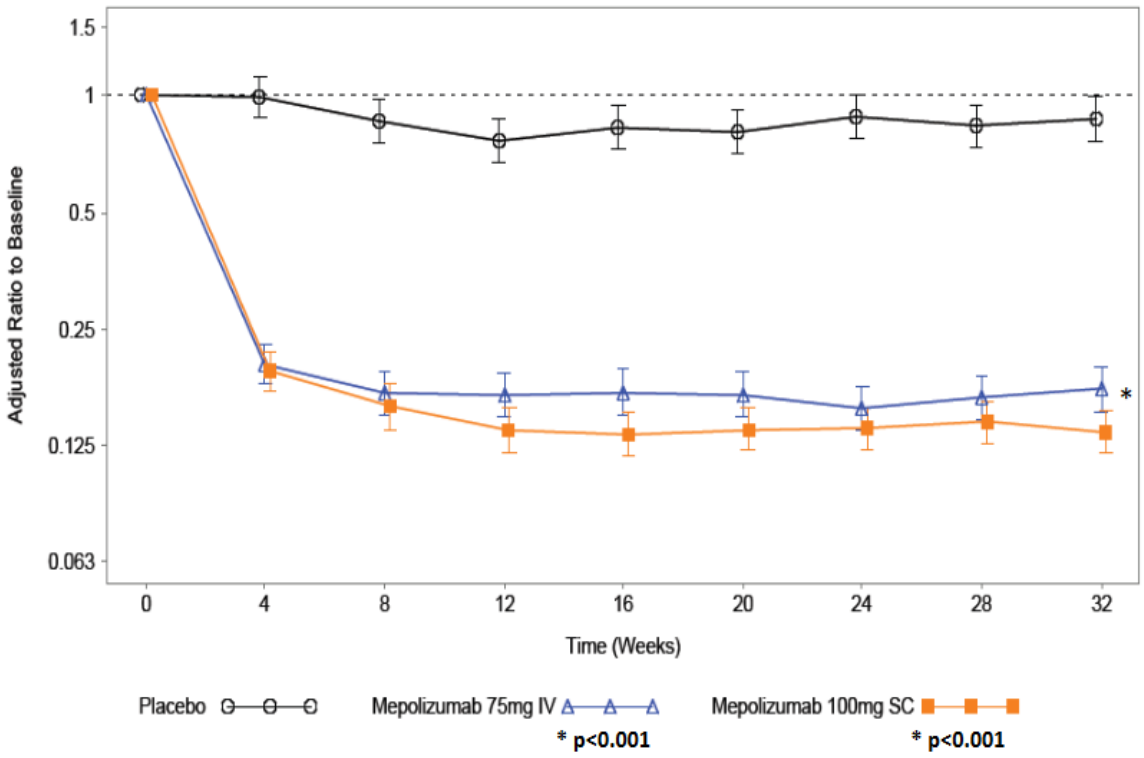
B.3.6.2 Mepolizumab MEA115588 (MENSA): Secondary outcome measures at week 32

A mixed model repeated measures method was used to analyse secondary outcome measure data.[8]

B.3.6.2.1 Blood eosinophil count

Blood eosinophil counts were similar in the three groups at baseline, with a geometric mean of 295 cells per µL. Mepolizumab decreased the eosinophil counts by week 4; the counts reached a nadir around week 12 (with reductions of 83% in the IV group and 86% in the SC group), and the decreases were maintained during the study (Figure 10).

Figure 10 Changes in blood eosinophil count from baseline to week 32[8]

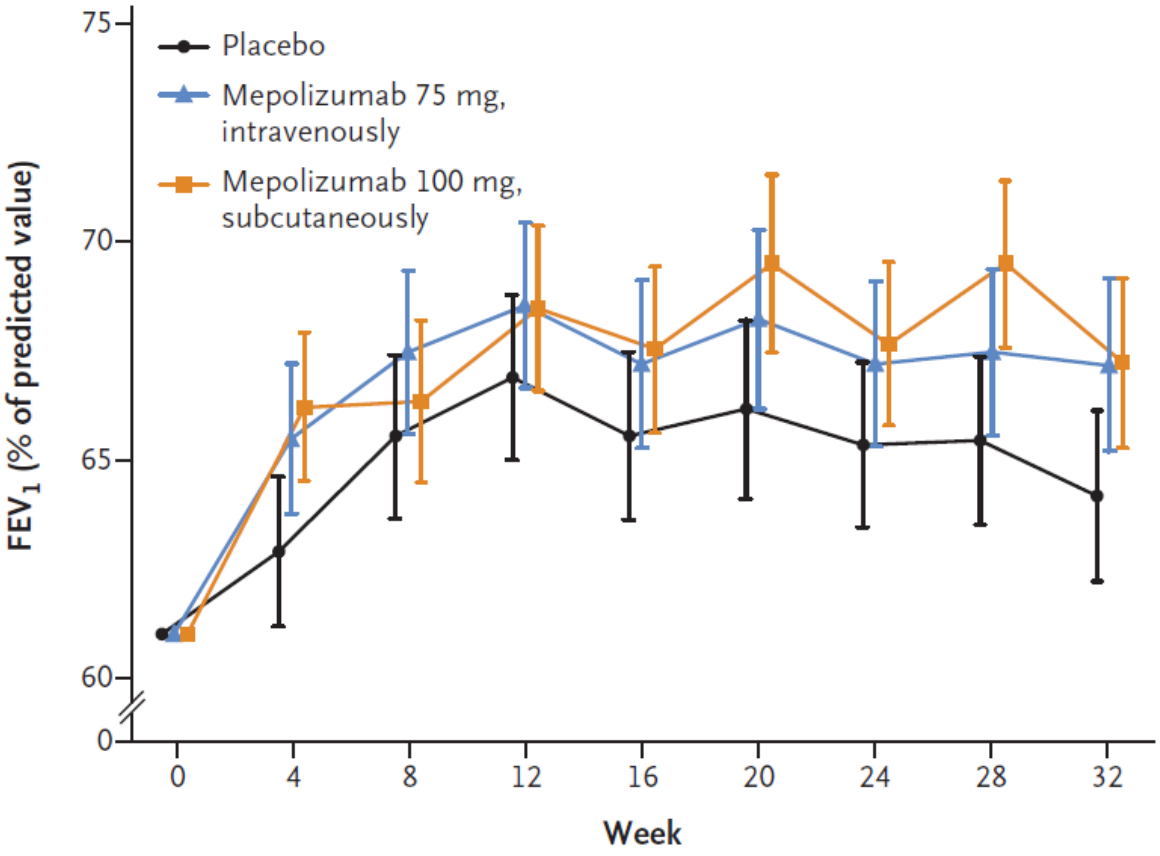


Abbreviations: IV; intravenous, SC; subcutaneous

B.3.6.2.2 Change in FEV_1

At week 32, the mean increase from baseline in FEV_1 before bronchodilation was 100 mL greater in the IV mepolizumab group than in the placebo group (p=0.02), and 98 mL greater in the SC mepolizumab group than in the placebo group (p=0.03) (Table 17 and Figure 11). The mean increase from baseline in FEV_1 after bronchodilation was 146 mL greater in the IV mepolizumab group than in the placebo group (p=0.003) and 138 mL greater in the SC mepolizumab group than in the placebo group (p=0.004) (Table 17). At week 32, the daily morning peak expiratory flow rate increased by 22.9 L per minute in the IV mepolizumab group, by 29.5 L per minute in the SC mepolizumab group and by 1.8 L per minute in the placebo group.

Figure 11 Mean FEV_1 as a percentage of the predicted value[8]



I bars indicate 95% CIs.
Abbreviations: CI; confidence interval, FEV_1; forced expiratory volume in 1 second

Table 17 Change in lung function from baseline[8]

Change from baseline in FEV_1, mL	Placebo group (n=191)	IV mepolizumab (n=191)	SC mepolizumab (n=194)
Before bronchodilation (± SE)	86 ± 31	186 ± 32	183 ± 31
Difference from placebo (95% CI)	–	100 (13, 187) p=0.02	98 (11, 184) p=0.03
After bronchodilation (± SE)	30 ± 34	176 ± 34	167 ± 33
Difference from placebo (95% CI)	–	146 (50, 242) p=0.003	138 (43, 232) p=0.004
Abbreviations: CI; confidence interval, FEV_1; forced expiratory volume in 1 second, IV; intravenous, SC; subcutaneous, SE; standard error			

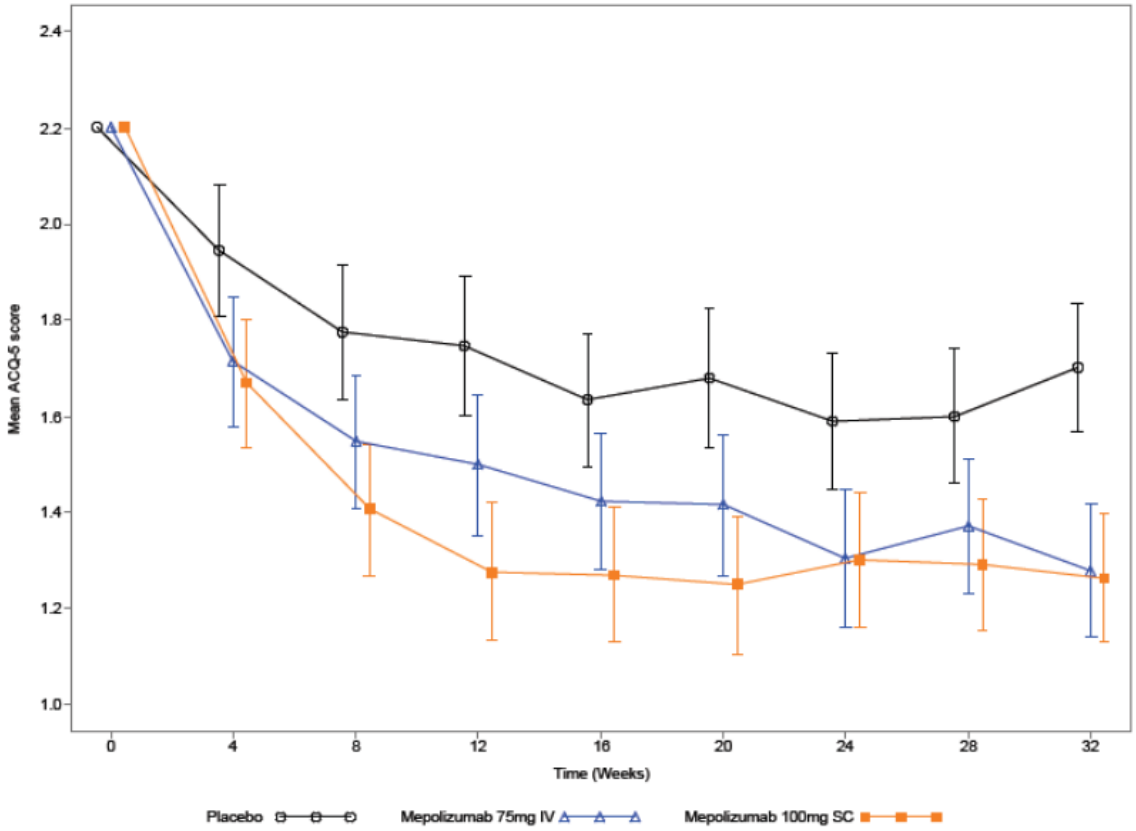
B.3.6.2.3 Asthma control based on the ACQ-5 score

At baseline, patients in the three study groups had similar mean ACQ-5 scores (2.12 in the IV mepolizumab group, 2.26 in the SC mepolizumab group and 2.28 in the placebo group), indicating uncontrolled asthma. At week 4 and continuing through week 32, patients in the two mepolizumab groups had greater improvement (i.e. a numerical decrease) from baseline in ACQ-5 scores, as compared with placebo. At week 32, the mean reductions in total scores were 0.42 points greater in the IV mepolizumab group and 0.44 points greater in the SC mepolizumab group than in the placebo group (p<0.001 for both comparisons) (Table 18 and Figure 12).

Table 18 Change from baseline in ACQ-5 score[8]

	Placebo group (n=191)	IV mepolizumab (n=191)	SC mepolizumab (n=194)
Change from baseline in score on ACQ	–0.50 ± 0.07	–0.92 ± 0.07	–0.94 ± 0.07
Difference from placebo (95% CI)	–	–0.42 (–0.61, –0.23) p<0.001	–0.44 (–0.63, –0.25) p<0.001
Abbreviations: ACQ; Asthma Control Questionnaire, CI; confidence interval, IV; intravenous, SC; subcutaneous			

Figure 12 Changes from baseline in ACQ-5[8]



Abbreviations: ACQ; Asthma Control Questionnaire, IV; intravenous, SC; subcutaneous

The five questions enquire about the frequency and/or severity of symptoms over the previous week. Scores range from 0–6, with lower scores indicating better control of asthma and a minimally important difference of 0.5. Bars represent 95% CI. Values are adjusted for covariates.

B.3.6.3 Mepolizumab MEA112997 (DREAM): Primary efficacy outcome – rate of clinically significant asthma exacerbations at week 52

During the study, 806 exacerbations requiring use of OCS, admission or a visit to an ED were reported.[20]

Compared with placebo, 75 mg mepolizumab reduced the number of clinically significant exacerbations per patient per year by 48% (95% CI: 31, 61; p<0.0001), 250 mg mepolizumab by 39% (95% CI: 19, 54; p=0.0005) and 750 mg mepolizumab by 52% (95% CI: 36, 64; p<0.0001) (Figure 13, Table 19). Additionally, 75 mg (hazard ratio [HR]: 0.45; 95% CI: 0.33, 0.61; p<0.0001), 250 mg (HR: 0.60; 95% CI: 0.45, 0.80; p=0.0005) and 750 mg (HR: 0.46; 95% CI: 0.34, 0.63; p<0.0001) doses all delayed time to first exacerbation compared with placebo. Figure 14 shows distribution of the number of exacerbations.

Figure 13 Cumulative number of exacerbations over time[20]

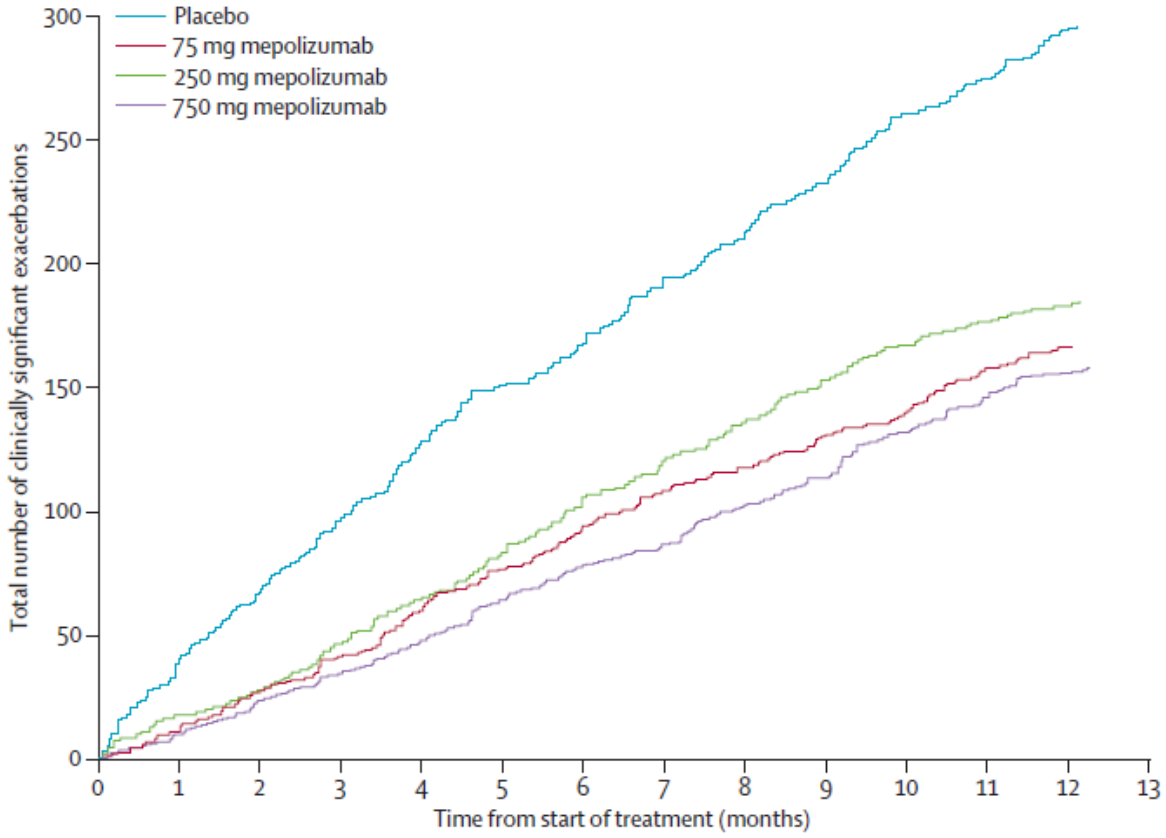
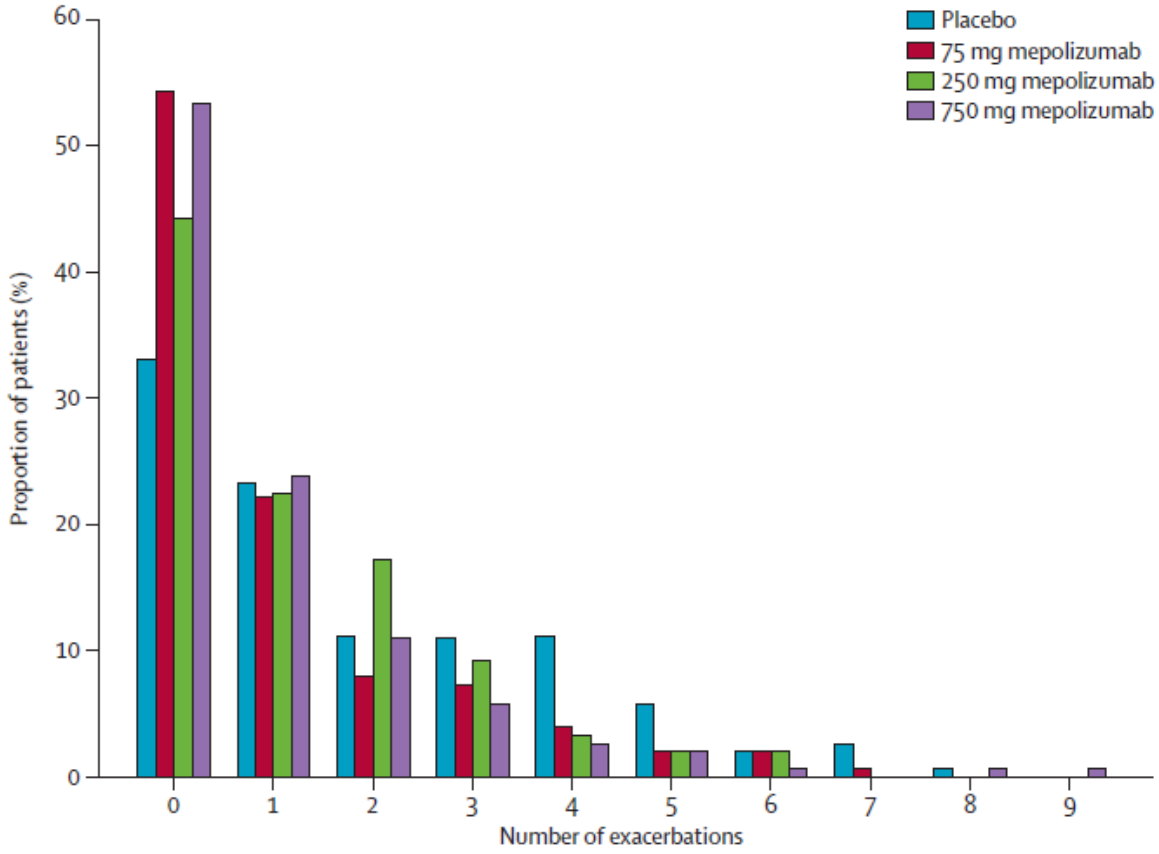


Table 19 Summary of primary efficacy outcome at week 52[20]

	Placebo group (n=155)	75 mg mepolizumab group (n=153)	250 mg mepolizumab group (n=152)	750 mg mepolizumab group (n=156)
Rate of clinically significant exacerbations per patient per year (SE logs)	2.40 (0.11)	1.24 (0.12)	1.46 (0.11)	1.15 (0.12)
Ratio to placebo (95% CI)	–	0.52 (0.39, 0.69)	0.61 (0.46, 0.81)	0.48 (0.36, 0.64)
Abbreviations: CI; confidence interval, SE; standard error				

Figure 14 Distribution of number of exacerbations[20]



B.3.6.4 Mepolizumab MEA112997 (DREAM): Secondary outcome measures at week 52

B.3.6.4.1 Rate of exacerbations requiring hospitalisation or ED visit

Exacerbations requiring admission or visits to an ED were reduced in all groups given mepolizumab compared with placebo (Table 20); 27 exacerbations in the placebo group required admission, as did 15 in the 75 mg mepolizumab, 17 in the 250 mg mepolizumab and 10 in the 750 mg mepolizumab groups.[20]

Table 20 Rate of exacerbations requiring hospital admission or ED visit[20]

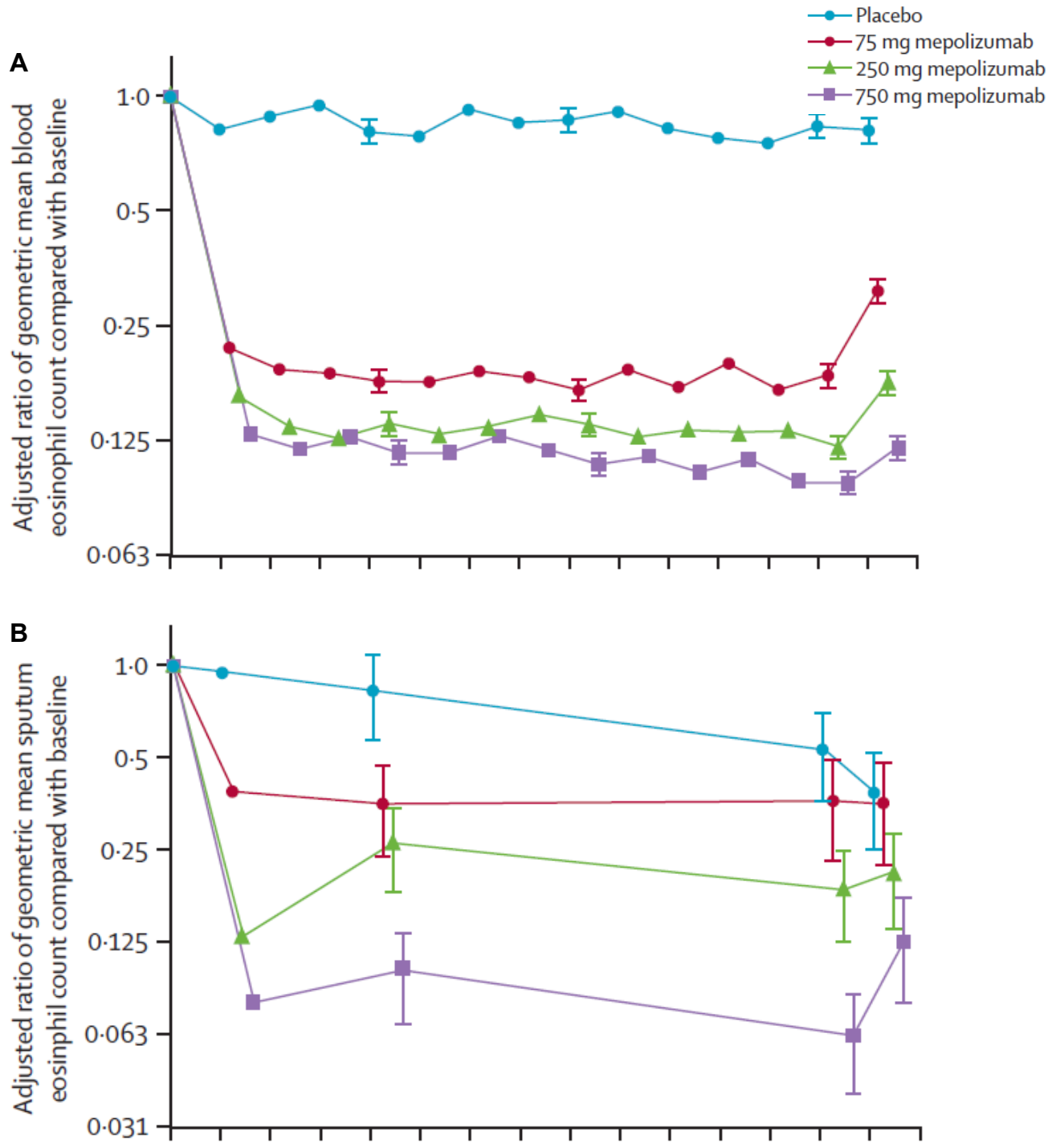
	Placebo n=155	**Mepolizumab 75 mg n=153**	**Mepolizumab 250 mg n=152**	**Mepolizumab 750 mg n=156**
Requiring hospitalisation or ED visit				
Exacerbation rate/year	0.43	0.17	0.25	0.22
Comparison vs placebo				
Rate ratio (mepolizumab/placebo)	–	0.40	0.58	0.52
95% CI	–	(0.19, 0.81)	(0.30, 1.12)	(0.27, 1.02)

	Placebo n=155	Mepolizumab 75 mg n=153	Mepolizumab 250 mg n=152	Mepolizumab 750 mg n=156
p-value	–	0.011		
Requiring hospitalisation				
Exacerbation rate/year	0.18	0.11	0.12	0.07
Comparison vs placebo				
Rate ratio (mepolizumab/placebo)	–	0.61	0.65	0.37
95% CI	–	(0.28, 1.33)	(0.31, 1.39)	(0.16, 0.88)
p-value	–	0.214		
Abbreviations: CI; confidence interval, ED; emergency department				

B.3.6.4.2 Blood and sputum eosinophil counts

Compared with placebo, the ratios of geometric means at 52 weeks showed that blood eosinophil counts were reduced in individuals given 75 mg mepolizumab (0.22; 95% CI: 0.18, 0.27; p<0.0001), 250 mg mepolizumab (0.14; 95% CI: 0.12, 0.18; p<0.0001) and 750 mg mepolizumab (0.12; 95% CI: 0.09, 0.14; p<0.0001) (Figure 15). In the subgroup of 94 patients who had sputum induction, sputum eosinophil counts were also decreased compared with placebo in individuals given 75 mg mepolizumab (ratio: 0.68; 95% CI: 0.13, 3.52; p=0.6429), 250 mg mepolizumab (ratio: 0.35; 95% CI: 0.08, 1.52; p=0.1577) and 750 mg mepolizumab (ratio: 0.12; 95% CI: 0.02, 0.56; p=0.0082).

Figure 15 Adjusted ratio of eosinophil count in blood (A) and sputum (B) compared with baseline[20]



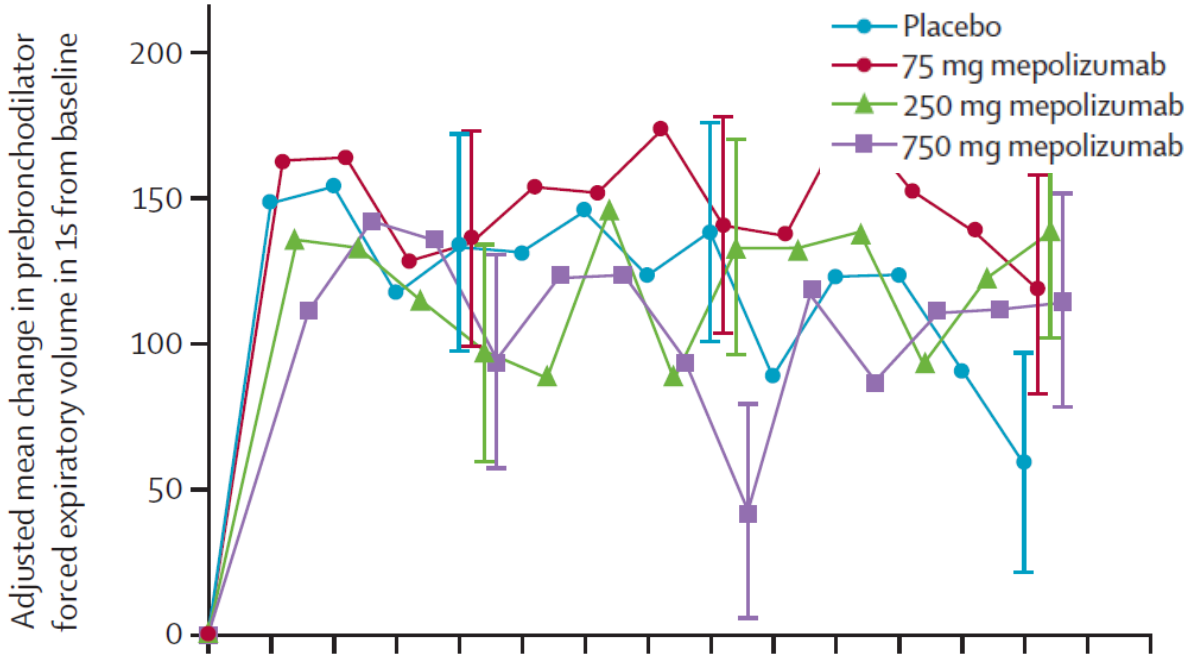
B.3.6.4.3 Pre-bronchodilator FEV_1

Table 21 and Figure 16 show that although there were some increases in pre-bronchodilator FEV_1, these changes were not statistically significant. Traditional markers of asthma such as FEV_1 and acute bronchodilator response did not reflect the efficacy of mepolizumab.

Table 21 Change in pre-bronchodilator FEV1 at week 52, and difference compared with placebo[20]

	Change in pre-bronchodilator FEV_1 at week 52, mL; mean (SE)	Difference from placebo, mL
Placebo n=155	60 (38)	-
Mepolizumab 75 mg n=153	121 (38)	61 (95% CI: –39, 161; p=0.229)
Mepolizumab 250 mg n=152	140 (37)	81 (95% CI: –19, 180)
Mepolizumab 750 mg n=156	115 (37)	56 (95% CI: –43, 155)
Abbreviations: CI; confidence interval, FEV_1; forced expiratory volume in 1 second, SE; standard error		

Figure 16 Change in pre-bronchodilator FEV_1 from baseline to 52 weeks[20]



Abbreviations: FEV_1; forced expiratory volume in 1 second

B.3.6.4.4 Change in ACQ score from baseline to week 52

Table 22 shows small reductions in ACQ scores that did not differ significantly from those reported with placebo.

Table 22 Change in ACQ score from baseline to week 52 versus placebo[20]

	Placebo n=155	Mepolizumab 75 mg n=153	Mepolizumab 250 mg n=152	Mepolizumab 750 mg n=156
Change in score, mean (SE)	–0.59 (0.09)	–0.75 (0.09)	–0.87 (0.09)	–0.80 (0.09)
Difference from placebo (95% CI)	–	–0.16 (–0.39, 0.07)	–0.27 (–0.51, 0.04)	–0.20 (–0.43, 0.03)
Abbreviations: ACQ; Asthma Control Questionnaire, CI; confidence interval, SE; standard error				

B.3.6.5 Mepolizumab MEA115575 (SIRIUS): Primary efficacy outcome – reduction in glucocorticoid dose at 20 weeks compared with placebo

The primary outcome was the degree of reduction in the glucocorticoid dose compared with the dose in the OCS optimisation phase, based on the following categories: 90–100% reduction; 75–<90% reduction; 50–<75% reduction; >0–<50% reduction; or no decrease in oral glucocorticoid dose, a lack of asthma control during weeks 20–24 or withdrawal from treatment.[32]

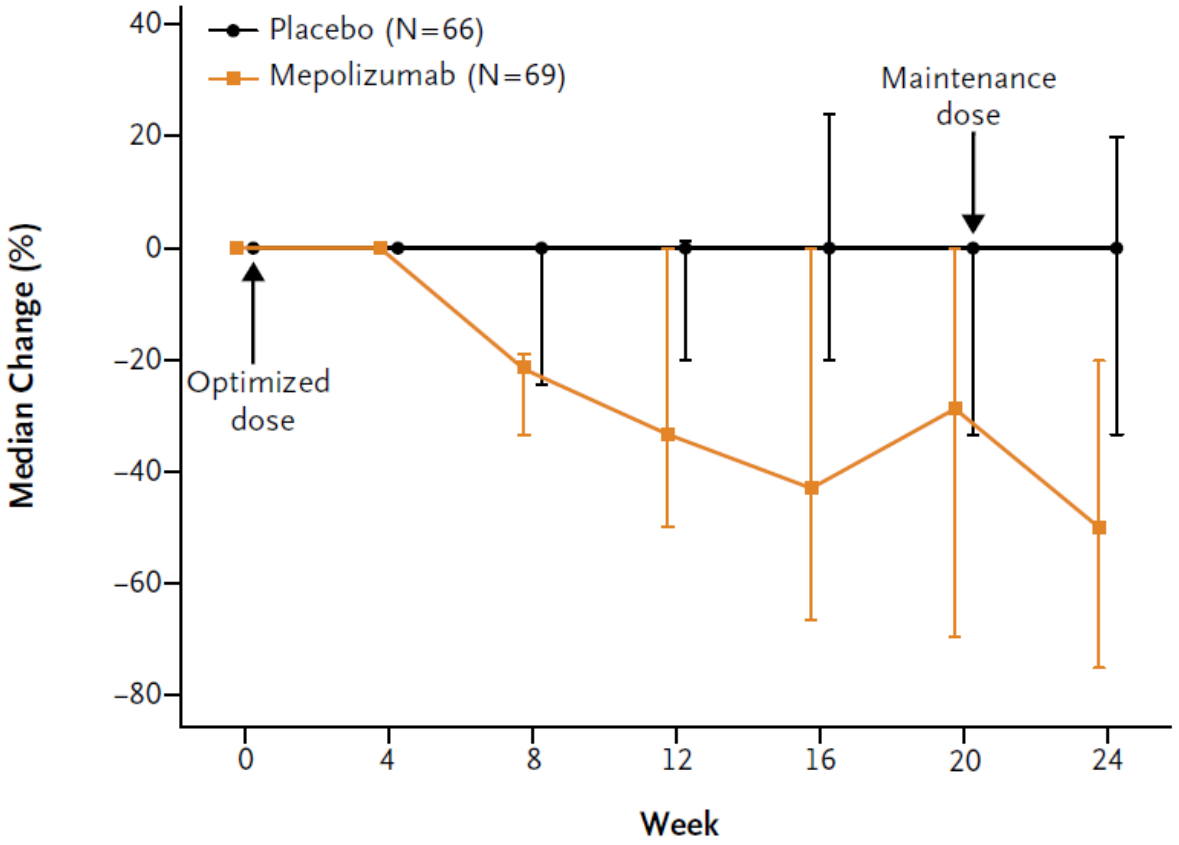
More patients in the mepolizumab group than in the placebo group had a reduction of 90–100% in the oral glucocorticoid dose (23% vs 11%) and a reduction of 70–<90% (17% vs 8%). In contrast, more patients in the placebo group than in the mepolizumab group had no reduction in the oral glucocorticoid dose, had a lack of asthma control or withdrew from the study (56% vs 36%). These analyses resulted in an overall odds ratio for a reduction in the oral glucocorticoid dose category in the mepolizumab group of 2.39 (95% CI: 1.25, 4.56; p=0.008) (Table 23). The median percentage reduction from baseline in the daily oral glucocorticoid dose was 50% among patients in the mepolizumab group, compared with no reduction among those in the placebo group (p=0.007) (Figure 17).

Table 23 Summary of oral glucocorticoid dose reduction at week 24[32]

Reduction in oral glucocorticoid dose at 20–24 weeks, n (%)*	Placebo (n=66)	Mepolizumab (n=69)
90–100%	7 (11)	16 (23)
75–<90%	5 (8)	12 (17)
50–<75%	10 (15)	9 (13)
>0–<50%	7 (11)	7 (10)
No decrease in oral glucocorticoid dose, lack of asthma control or withdrawal from treatment	37 (56)	25 (36)
*Odds ratio: 2.39 (95% CI: 1.25, 4.56); p=0.008 Odds ratio relates to the mepolizumab group as compared with the placebo group Abbreviation: CI; confidence interval		

Figure 17 shows that at 24 weeks, the median percentage reduction in daily glucocorticoid dose was 50% in the mepolizumab group, and there was no reduction in the placebo group (p=0.007).

Figure 17 Median percentage reduction from baseline in daily glucocorticoid dose[28]



Bars represent 95% CIs
Abbreviation: CI; confidence interval

B.3.6.6 Mepolizumab MEA115575 (SIRIUS): Secondary outcome measures

B.3.6.6.1 Annualised rate of clinically significant exacerbations to week 24

Despite receiving a reduced glucocorticoid dose, patients in the mepolizumab group, as compared with those in the placebo group, had a relative reduction of 32% in the annualized rate of exacerbations (1.44 vs 2.12, p=0.042; Table 24).[32]

Table 24 Rate of clinically significant exacerbations in mepolizumab versus placebo[32]

Clinically significant exacerbations	Placebo n=66	Mepolizumab 100 mg SC n=69
Exacerbation rate/year	2.12	1.44
Rate ratio (mepolizumab/placebo)	–	0.68
95% CI	–	0.47, 0.99
p-value	–	0.042
Abbreviations: CI; confidence interval, SC; subcutaneous		

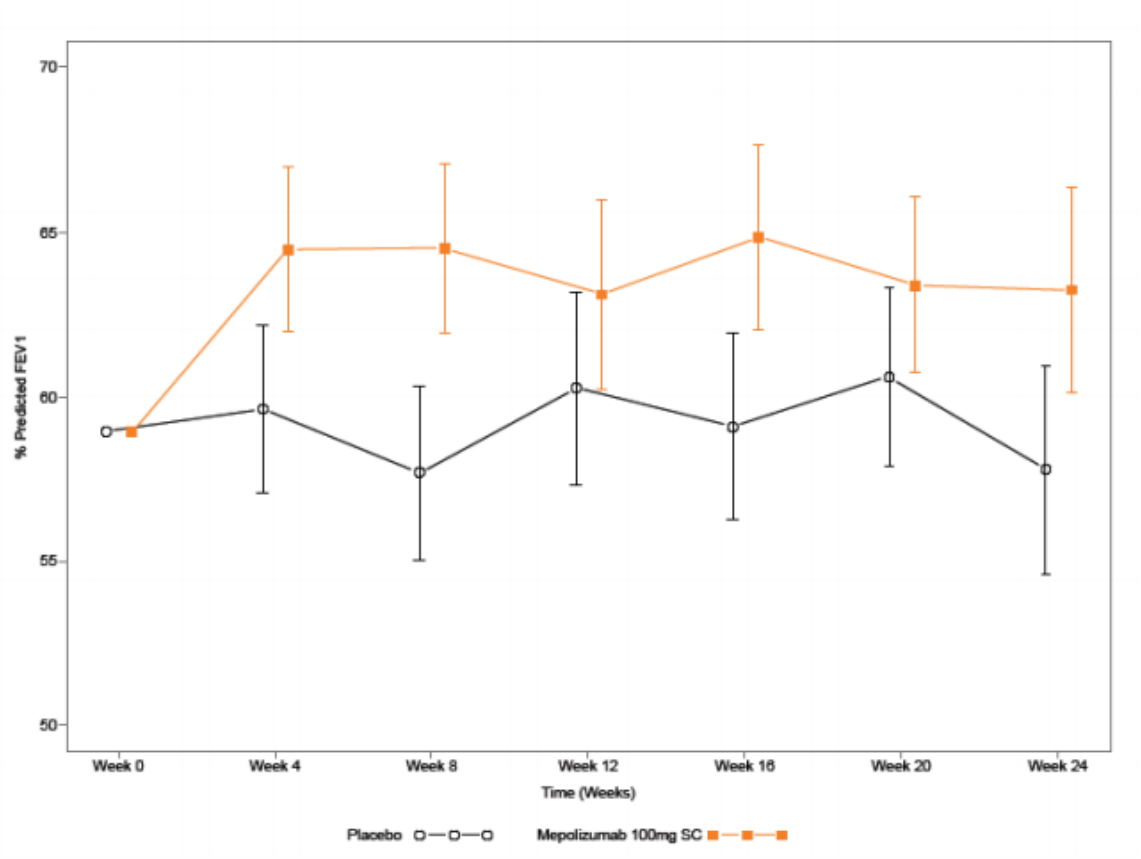
B.3.6.6.2 Mean change from baseline in clinic pre-bronchodilator FEV_1 and in clinic post-bronchodilator FEV_1 at week 24

Table 25 and Figure 18 shows that improvement in lung function (FEV_1) was observed at the end of the study.

Table 25 Analysis of change from baseline in pre- and post-bronchodilator FEV_1 at week 24 (ITT population)[32]

FEV_1 (mL)	Mepolizumab vs placebo
Pre-bronchodilator FEV_1	
Difference	114
p-value	0.151
Post-bronchodilator FEV_1	
Difference	128
p-value	0.064
Abbreviations: FEV_1; forced expiratory volume in 1 second, ITT; intention-to-treat	

Figure 18 Changes from baseline in pre-bronchodilator FEV_1 percent of predicted value[32]

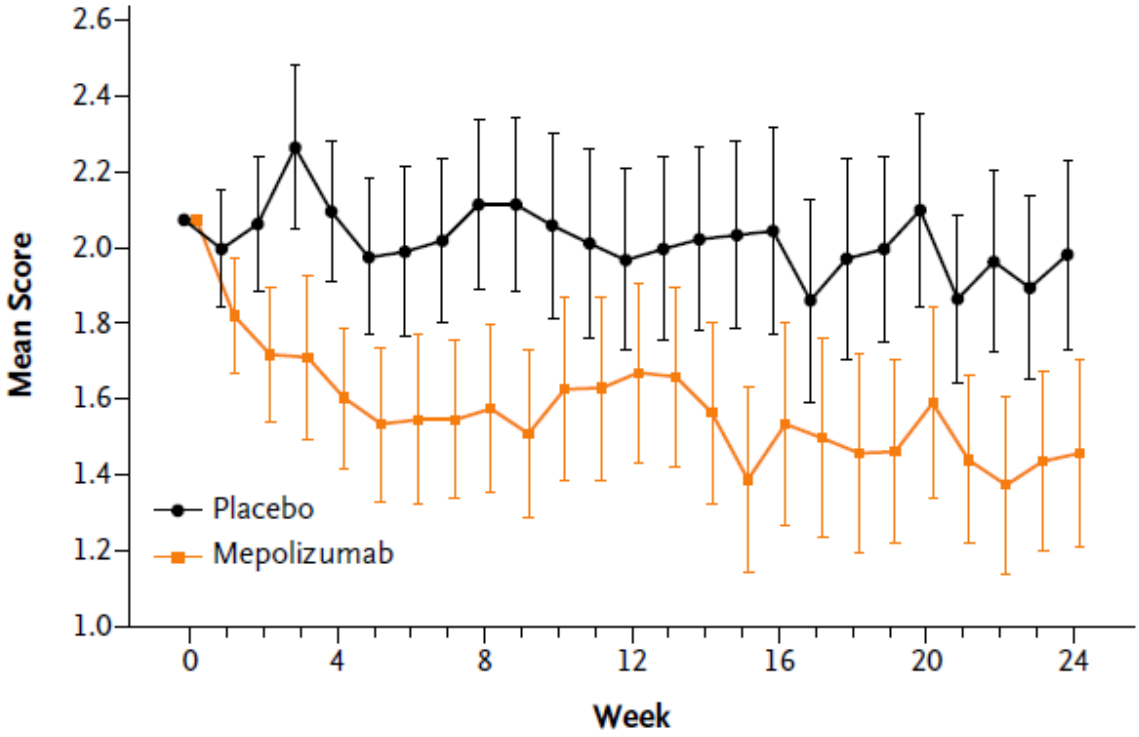


Values are adjusted for covariates
Abbreviations: FEV_1; forced expiratory volume in 1 second, SC; subcutaneous

B.3.6.6.3 Change in ACQ-5 score

Figure 19 shows patients in the mepolizumab group had reduction of 0.52 points with respect to asthma symptoms (p=0.004), as measured on the ACQ-5 (in which the minimal clinically important difference is 0.5 points). Improvements were observed as early as week 2 in the mepolizumab group, an effect that was sustained up to week 24 (p=0.004).

Figure 19 Change in ACQ-5 score over 24 weeks[32]

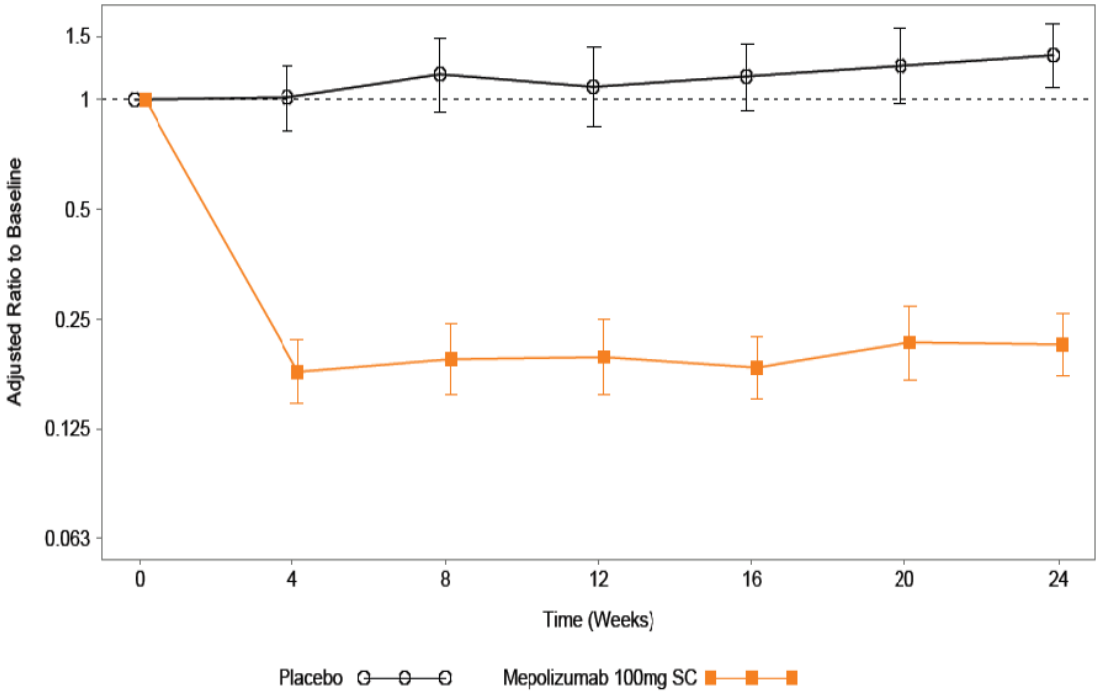


Abbreviations: ACQ; Asthma Control Questionnaire

B.3.6.6.4 Blood eosinophil count

As compared with placebo, mepolizumab significantly reduced blood eosinophil counts throughout the study ($p<0.001$) (Figure 20)

Figure 20 Blood eosinophil count over 24 weeks[32]



Abbreviations: FEV_1; forced expiratory volume in 1 second, SC; subcutaneous

B.3.6.7 Mepolizumab MUSCA: Secondary efficacy outcomes – mean change from baseline in ACQ-5 score and mean change in pre-bronchodilator FEV_1 at Week 24

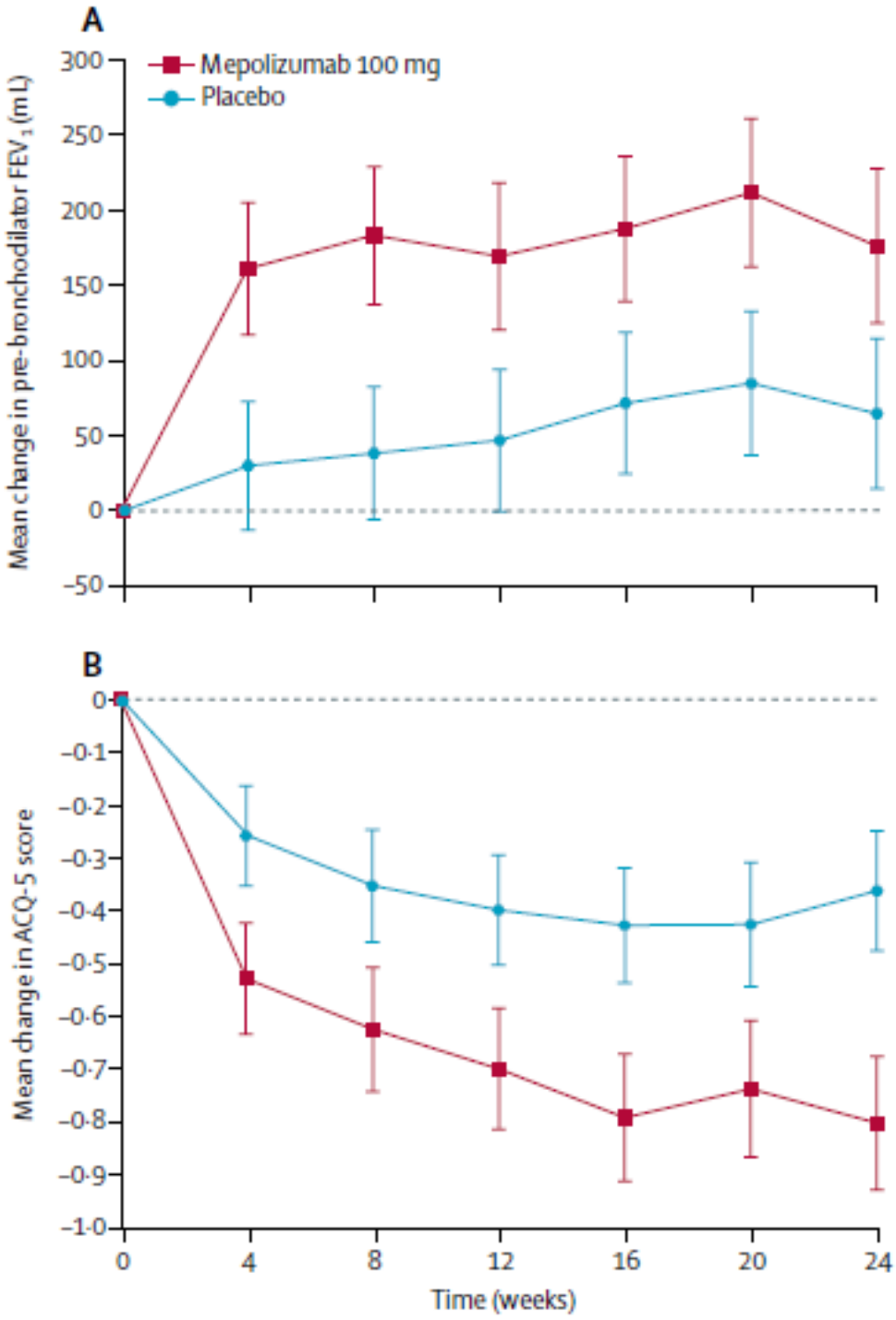
The primary efficacy endpoint of the MUSCA study was change in patient health-related quality of life, measured as change from baseline in SGRQ total score at week 24. The key secondary endpoints included functional changes from baseline to week 24 in pre-bronchodilator FEV_1, the proportion of SGRQ total score responders and mean change from baseline in ACQ-5 score.

B.3.6.7.1 Change in ACQ-5 score

The mean change from baseline in ACQ-5 score at week 24 was greater for patients treated with mepolizumab 100 mg SC compared with placebo. The mean treatment difference between placebo and mepolizumab at week 24 was –0.4 (95% CI: –0.6, –0.2; p<0.0001), with between-group differences in ACQ-5 change from baseline evident from week 4 onwards (Figure 21).

Furthermore, a significantly greater proportion of patients were ACQ-5 responders (defined as patients achieving a reduction of ≥0.5 points from baseline in ACQ-5 score) following treatment with mepolizumab versus placebo (161/274 vs 116/276), respectively; treatment difference: 2.0 (95% CI: 1.4, 2.8; p=0.0014).

Figure 21 Adjusted mean changes (95% CI) from baseline in (A) pre-bronchodilator FEV_1 and (B) ACQ-5[33]



Abbreviations: ACQ; Asthma Control Questionnaire, CI; confidence interval, FEV_1; forced expiratory volume in 1 second

B.3.6.7.2 Changes in lung function

Mean changes from baseline in pre-bronchodilator FEV_1, forced vital capacity (FVC) and $FEF_{25–75}$ (forced expiratory flow at 25–75% of FVC) at week 24 were significantly greater for patients treated with mepolizumab 100 mg SC versus placebo (Table 26). Pre-bronchodilator FEV_1 values improved early, and improvements were sustained

up to week 24 (Figure 21). Mean changes from baseline in post-bronchodilator FEV_1 and FVC were non-significantly higher at week 24 with mepolizumab versus placebo (data not shown).

The mean annualised rates of clinically significant exacerbations, as well as exacerbations requiring an emergency room visit or admission to hospital, were significantly lower in the mepolizumab group versus the placebo group, resulting in yearly rate reductions of 58% and 68%, respectively. The annual rate of exacerbations requiring admission to hospital did not differ between groups.

Table 26 Functional endpoints of the MUSCA study[33]

	Placebo (n=277)	Mepolizumab (n=274)	Treatment difference (95% CI; p-value)
Pre-bronchodilator FEV_1 at week 24 (mL)			120 (47, 192; p=0.001)
Baseline pre-bronchodilator FEV_1	1,805 (660)	1,887 (709)	
Change from baseline	56 (26) [n=259]	176 (26) [n=264]	
Pre-bronchodilator FVC at week 24 (mL)			102 (23, 181; p=0.012)
Baseline pre-bronchodilator FVC	2,993 (913)	3,186 (971)	
Change from baseline	41 (28) [n=259]	143 (28) [n=264]	
Pre-bronchodilator $FEF_{25–75}$ at week 24 (mL/s)			123 (46, 200; p=0.002)
Baseline pre-bronchodilator $FEF_{25–75}$	998 (659)	1,017 (641)	
Change from baseline	44 (28) [n=259]	167 (28) [n=264]	

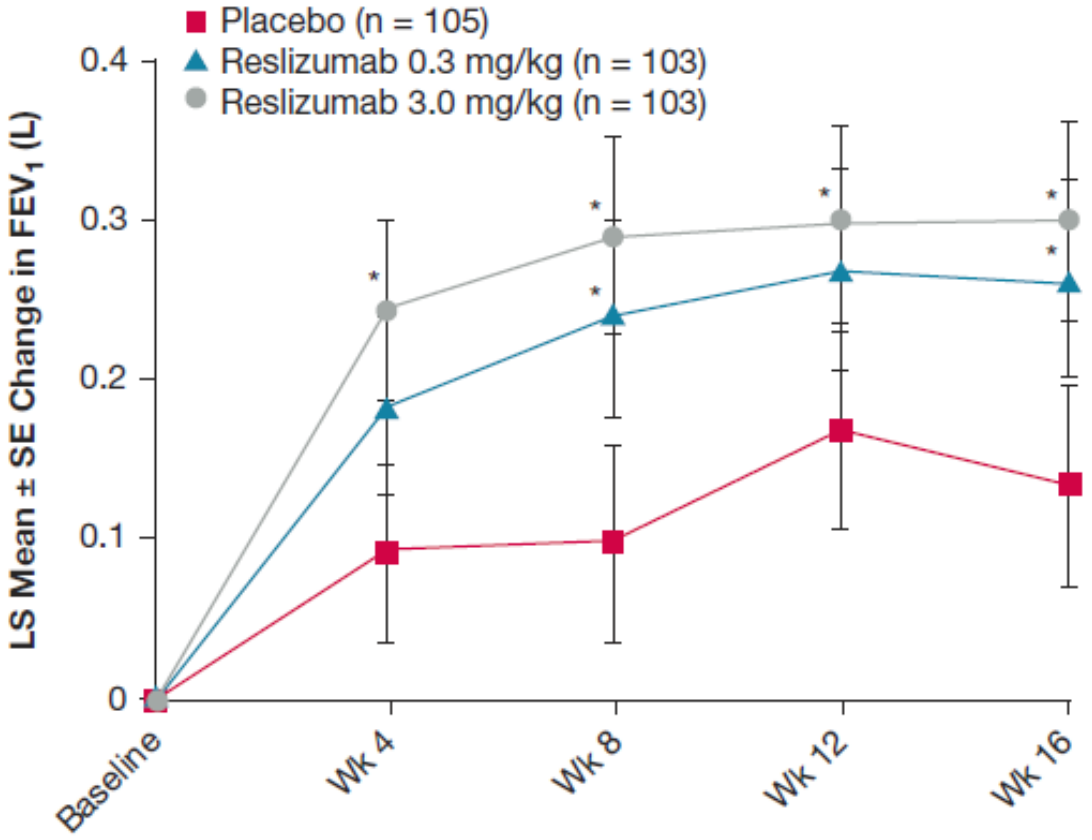
Abbreviations: CI; confidence interval, $FEF_{25–75}$; forced expiratory flow at 25–75% of FVC, FEV_1; forced expiratory volume in 1 second, FVC; forced vital capacity.

B.3.6.8 Reslizumab Study 3081: Primary efficacy outcome – change from baseline in pre-bronchodilator FEV_1 (over 16 weeks)

The primary objective was to determine whether reslizumab 0.3 mg/kg or 3.0 mg/kg improved FEV_1 compared with placebo over 16 weeks in patients with persistent asthma and elevated blood eosinophil levels. The primary analysis was conducted in the FAS, consisting of all randomised patients who received ≥1 dose of the study drug.

Overall change in FEV_1 over 16 weeks improved significantly with reslizumab 0.3 mg/kg (115 mL; p=0.0237) and 3.0 mg/kg (160 mL; p=0.0018) compared with placebo (Figure 22, Table 27). FEV_1 improved as early as 4 weeks with reslizumab 3.0 mg/kg versus placebo (treatment difference, 153 mL), and this improvement was maintained for the duration of the study.

Figure 22 Change in FEV_1 over 16 weeks



*p≤0.05 versus placebo
Only week 16 was controlled for type 1 error; all other p-values were not adjusted to control for multiplicity
Abbreviations: FEV_1; forced expiratory volume in 1 second, LS; least squares, SE; standard error

Table 27 Change in FEV_1 over 16 weeks

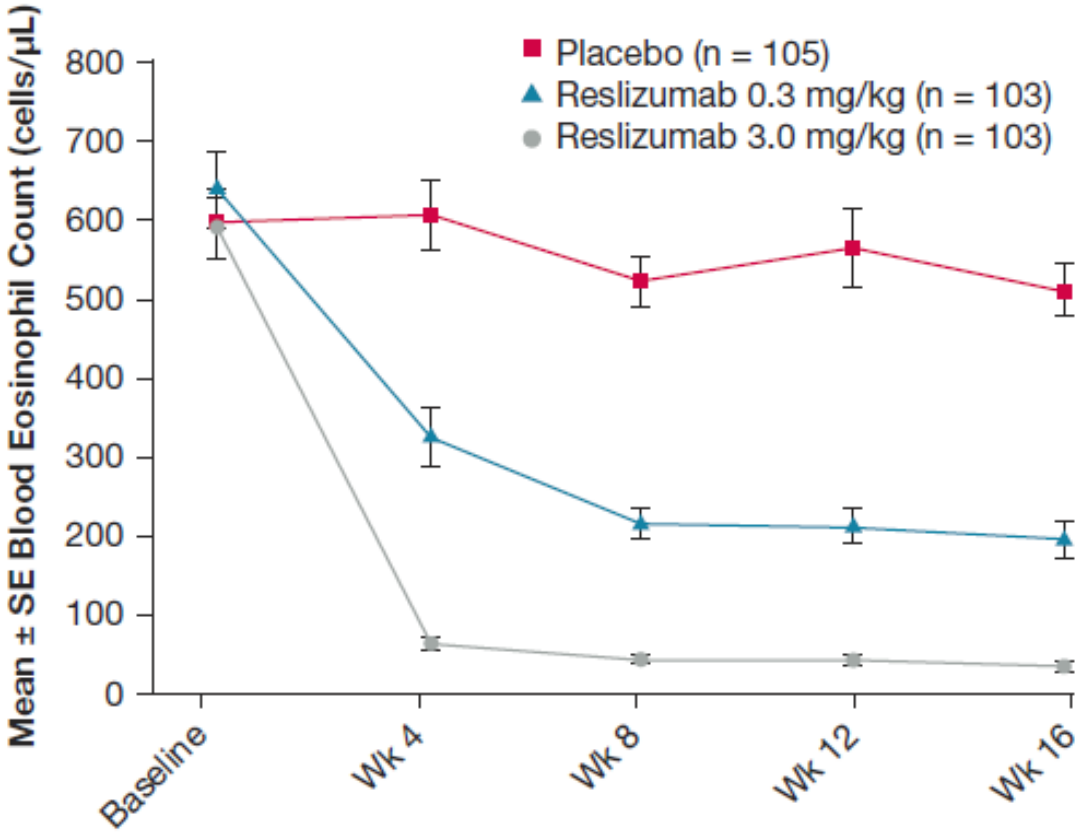
FEV_1 (L)	Placebo	Reslizumab 0.3 mg/kg	Reslizumab 3.0 mg/kg
N	103	101	102
LS mean ±SE	0.126 ±0.0549	0.242 ±0.0556	0.286 ±0.0548
Change (95% CI)		0.115 (0.016, 0.215)	0.160 (0.060, 0.259)
p-value		0.0237	0.0018
Abbreviations: CI; confidence interval, FEV_1; forced expiratory volume in 1 second, LS; least squares, SE; standard error			

B.3.6.9 Reslizumab Study 3081: Secondary outcome measures

B.3.6.9.1 Blood eosinophil count

Overall reductions in blood eosinophil levels were greater with reslizumab versus placebo, with the greatest decreases observed with the 3.0 mg/kg dose (Figure 23, Table 28)

Figure 23 Changes in blood eosinophil count



Abbreviations: SE; standard error

Table 28 Change in blood eosinophil count

Blood eosinophil level, cells/µL	Placebo	Reslizumab 0.3 mg/kg	Reslizumab 3.0 mg/kg
N	103	101	102
LS mean ±SE	–35 ±27.1	–358 ±27.7	–529 ±27.0
Change (95% CI)		–323 (–370, –275)	–494 (–542, –447)
p-value		0.0000	0.0000
Abbreviations: CI; confidence interval, LS; least squares, SE; standard error			

Baseline eosinophil levels ≥400 cells/µL (<500 [but ≥400], and ≥500 cells/µL) did not consistently influence the magnitude of improvements in FEV_1. The exception was a trend toward a larger treatment effect (compared with the overall effect) for the 3.0 mg/kg dose beginning at an eosinophil count ≥700 cells/µL. In addition, short-term variability in blood eosinophil counts (i.e. primary inclusion of ≥1 blood eosinophil count ≥400 cells/µL during screening versus ≥400 cells/µL at all assessments including baseline) had no notable effect on the primary efficacy outcome. However, it is important to note that the number of patients in the sensitivity analyses was low

(difference from placebo, 135 µL [≥1 blood eosinophil count <400 cells/µL during screening] vs 155 µL [all assessments ≥400 cells/µL]; 3.0 mg/kg reslizumab).

B.3.6.9.2 ACQ, ACQ-6, ACQ-5 scores

Improvements were seen across ACQ, ACQ-5 and ACQ-6 scores and were numerically greater for the 3.0 mg/kg dose.

Table 29 Change in ACQ scores

	Placebo (N=103)	**Reslizumab 0.3 mg/kg (N=101)**	**Reslizumab 3.0 mg/kg (N=101)**
ACQ			
LS mean ±SE	–0.494 ±0.1231	–0.732 ±0.1250	–0.853 ±0.1233
Change (95% CI)		–0.238 (–0.456, –0.019)	–0.359 (–0.577, –0.140)
p-value		0.0329	0.0014
ACQ-5			
LS mean	–0.568	–0.788	–0.917
Change (95% CI)		–0.220 (–4.60, 0.020)	–0.349 (–0.590, –0.109)
p-value		0.0726	0.0045
ACQ-6			
LS mean	–0.514	–0.751	–0.838
Change (95% CI)		–0.236 (–0.465, –0.007)	–0.323 (–0.553, –0.094)
p-value		0.043	0.0058
Abbreviations: ACQ; Asthma Control Questionnaire, CI; confidence interval, LS; least squares, SE; standard error			

B.3.6.10 Reslizumab Study 3082: Primary efficacy outcome – frequency of asthma exacerbations over 52 weeks

The primary endpoint was the frequency of clinical asthma exacerbations per patient during the 52-week treatment period, with events adjudicated by an independent review committee, assessed in the ITT population.
Reslizumab was associated with a reduction in the adjudicated clinical asthma exacerbation rate compared with placebo after more than 52 weeks (Table 30). Compared with placebo, treatment with reslizumab was associated with a 34% reduction in the frequency of clinical asthma exacerbation events needing hospital admission or ED treatment, but this was not significant.

Table 30 Change in clinically relevant exacerbation rate over 52 weeks

	Placebo (n=244)	**Reslizumab (n=245)**	**Rate ratio (95% CI)***	**p-value**
Patients with ≥1 clinically relevant exacerbation, n (%)	132 (54)	92 (38)	–	–
Adjudicated clinical asthma exacerbation rate (events per patient/per year)				

All events	1.80	0.90	0.50 (0.37, 0.67)	<0.0001
Events requiring systemic corticosteroids for ≥3 days	1.60	0.72	0.45 (0.33, 0.62)	<0.0001
Events requiring hospital admission or ED treatment	0.21	0.14	0.66 (0.32, 1.36)	0.257
*The rate ratio represents the ratio of adjudicated clinical asthma exacerbation rates between the reslizumab and placebo groups Abbreviations: CI; confidence interval, ED; emergency department				

B.3.6.11 Reslizumab Study 3082: Secondary outcome measures

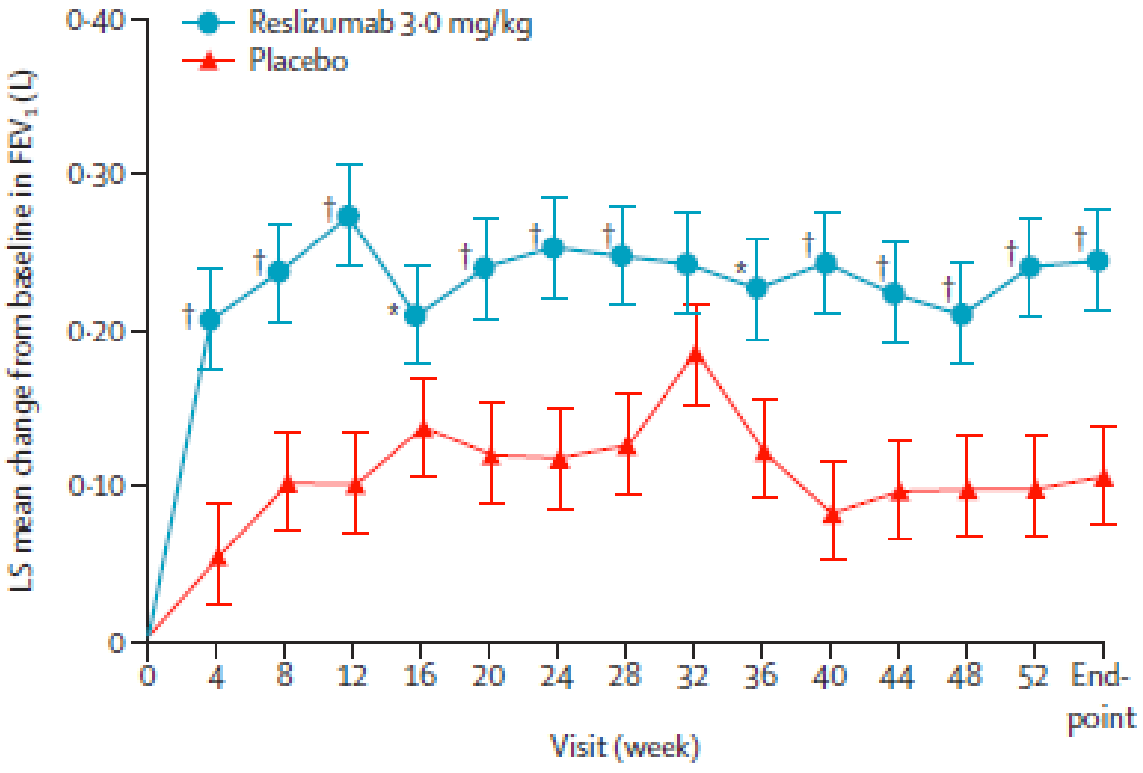
B.3.6.11.1 Change in FEV_1 from baseline over 16 weeks

An improvement in FEV_1 was evident for reslizumab versus placebo by the first on-treatment assessment at week 4, which was sustained through weeks 16 and 52 (Table 31, Figure 24).

Table 31 Change in FEV_1 over 16 and 52 weeks

Change in FEV_1 (L)	Placebo (n=244)	Reslizumab (n=245)	Rate ratio (95% CI)	p-value
Week 16	0.110	0.248	0.137 (0.08, 0.198)	<0.0001
Week 52	0.109	0.235	0.126 (0.06, 0.188)	<0.0001
Abbreviation: FEV_1; forced expiratory volume in 1 second				

Figure 24 Change in FEV_1 over 52 weeks



*p<0.05
†p<0.01
Abbreviations: FEV_1; forced expiratory volume in 1 second, LS; least squares

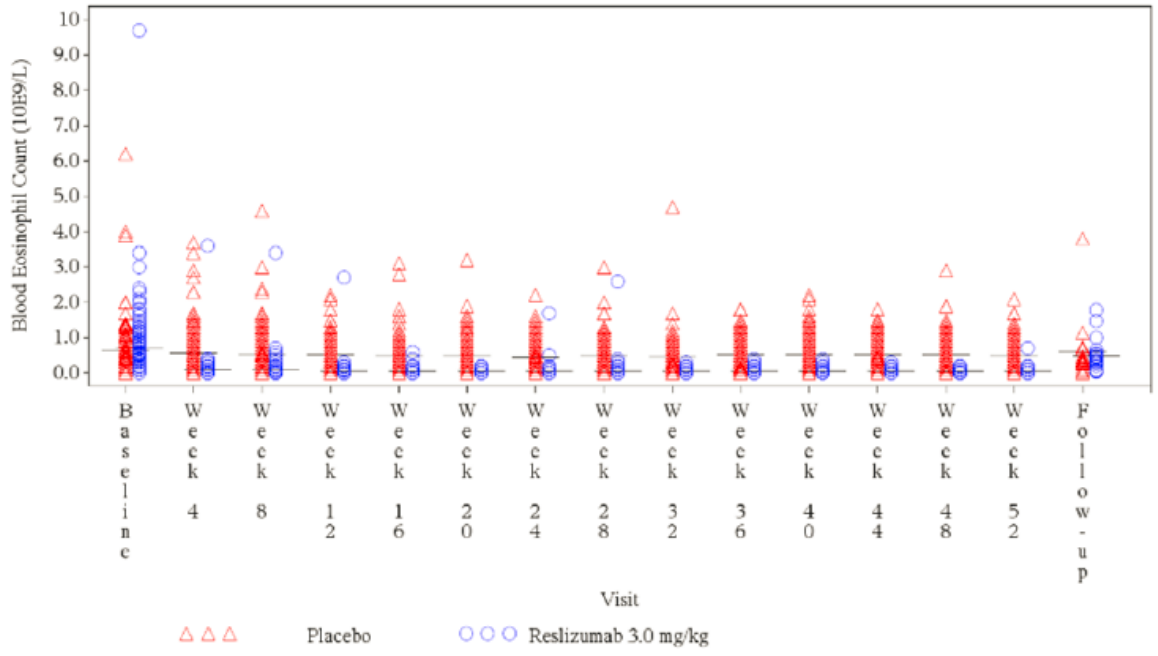
B.3.6.11.2 Change in blood eosinophil count

Reslizumab was associated with a reduction in blood eosinophil counts compared with placebo (Table 32), which was apparent by the first on-treatment assessment at week 4 and sustained for the duration of the studies (Figure 25). Blood eosinophils had substantially returned to baseline by the 90-day follow-up visit (90 days after treatment end or early withdrawal) in those patients who did not enrol into the reslizumab open-label safety extension.

Table 32 Change in blood eosinophil count over 16 and 52 weeks

Change in blood eosinophil count (cells/µL)	Placebo (n=244)	Reslizumab (n=245)	Rate ratio (95% CI)	p-value
Week 16	–118	–584	–466 (–514, –418)	<0.0001
Week 52	–127	–582	–455 (–491, –419)	<0.0001
Values shown are LS mean changes over the specified period from baseline. The between-group difference is the absolute reduction in the reslizumab group versus the placebo group Abbreviations: CI; confidence interval, LS; least squares				

Figure 25 Scatter plot of blood eosinophil count over the 52-week treatment period



B.3.6.11.3 Change in ACQ-7 score

The proportion of patients achieving a 0.5-point reduction in ACQ-7 score from baseline to end was significantly higher in the reslizumab group than in the placebo group (184 [76%] vs 152 [63%]; p=0.0002) (Table 33). Improvements were seen as

early as the first on-treatment assessment at week 4, and were sustained through to week 52.

Table 33 Change in ACQ-7 score

Change in ACQ-7 score	Placebo (n=244)	Reslizumab (n=245)	Rate ratio (95% CI)	p-value
Week 16	–0.68	–0.94	–0.27 (–0.40, –0.13)	0.0001
Week 52	–0.76	–1.02	–0.26 (–0.39, –0.12)	0.0002
Abbreviations: ACQ; Asthma Control Questionnaire, CI; confidence interval				

B.3.6.12 Reslizumab Study 3083: Primary efficacy outcome – frequency of asthma exacerbations over 52 weeks

The primary endpoint was the frequency of clinical asthma exacerbations per patient during the 52-week treatment period, with events adjudicated by an independent review committee, assessed in the ITT population.

Reslizumab was associated with a reduction in the adjudicated clinical asthma exacerbation rate compared with placebo after more than 52 weeks (Table 34). Compared with placebo, treatment with reslizumab was associated with a 31% reduction in the frequency of clinical asthma exacerbation events needing hospital admission or ED treatment, but this was not significant.

Table 34 Change in clinical asthma exacerbation rate over 52 weeks

	Placebo (n=232)	Reslizumab (n=232)	Rate ratio (95% CI)*	p-value
Patients with ≥1 clinical asthma exacerbation, n (%)	105 (45)	59 (25)	–	–
Adjudicated clinical asthma exacerbation rate (events per patient/per year)				
All events	2.11	0.86	0.41 (0.28, 0.59)	<0.0001
Events requiring systemic corticosteroids for ≥3 days	1.66	0.65	0.39 (0.26, 0.58)	<0.0001
Events requiring hospital admission or ED treatment	0.05	0.03	0.69 (0.29, 1.65)	0.402
*The rate ratio represents the ratio of adjudicated clinical asthma exacerbation rates between the reslizumab and placebo groups Abbreviations: CI; confidence interval, ED; emergency department				

B.3.6.13 Reslizumab Study 3083: Secondary outcome measures

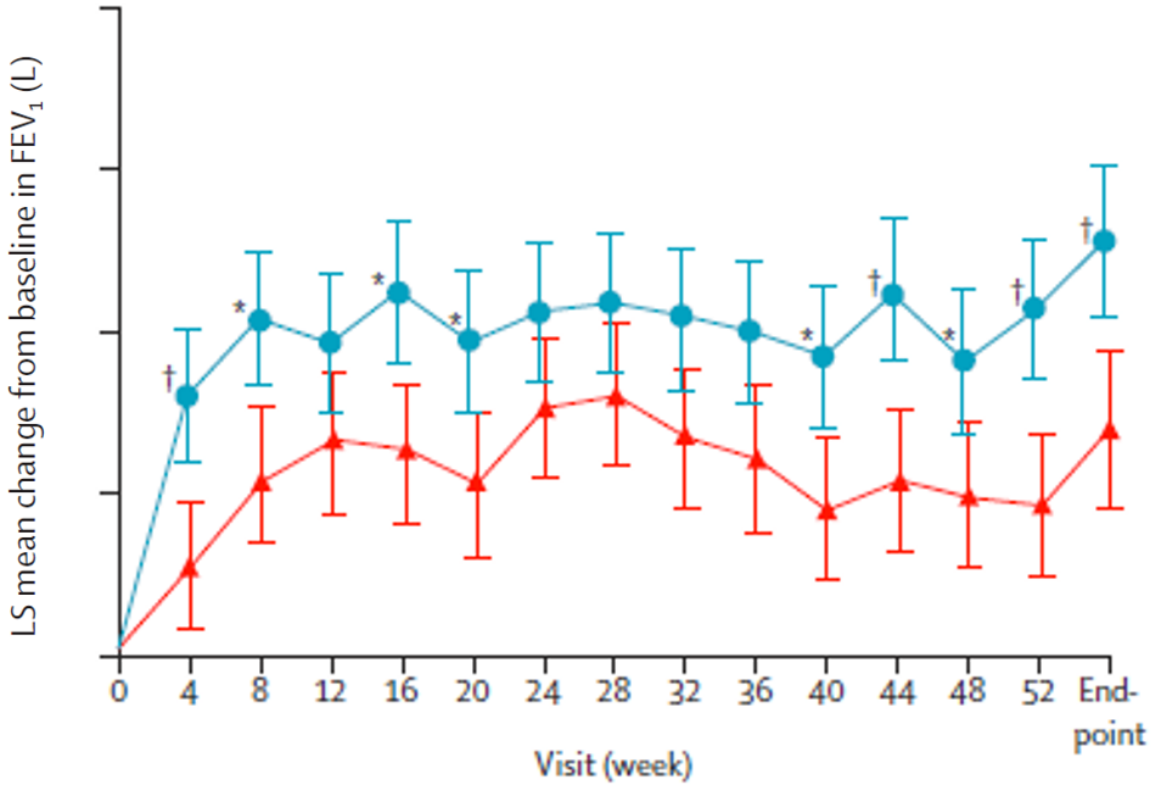
B.3.6.13.1 Change in FEV_1 from baseline over 16 weeks

An improvement in FEV_1 was evident for reslizumab versus placebo by the first on-treatment assessment at week 4, and was sustained through weeks 16 and 52 (Table 35, Figure 26).

Table 35 Change in FEV_1 over 16 and 52 weeks

Change in FEV_1 (L)	Placebo (n=232)	Reslizumab (n=232)	Rate ratio (95% CI)	p-value
Week 16	0.094	0.187	0.093 (0.003, 0.155)	0.0037
Week 52	0.111	0.201	0.090 (0.003, 0.153)	0.0057
Abbreviation: CI; confidence interval, FEV_1; forced expiratory volume in 1 second				

Figure 26 Change in FEV_1 over 52 weeks



*p<0.05
†p<0.01
Abbreviations: FEV_1; forced expiratory volume in 1 second, LS; least squares

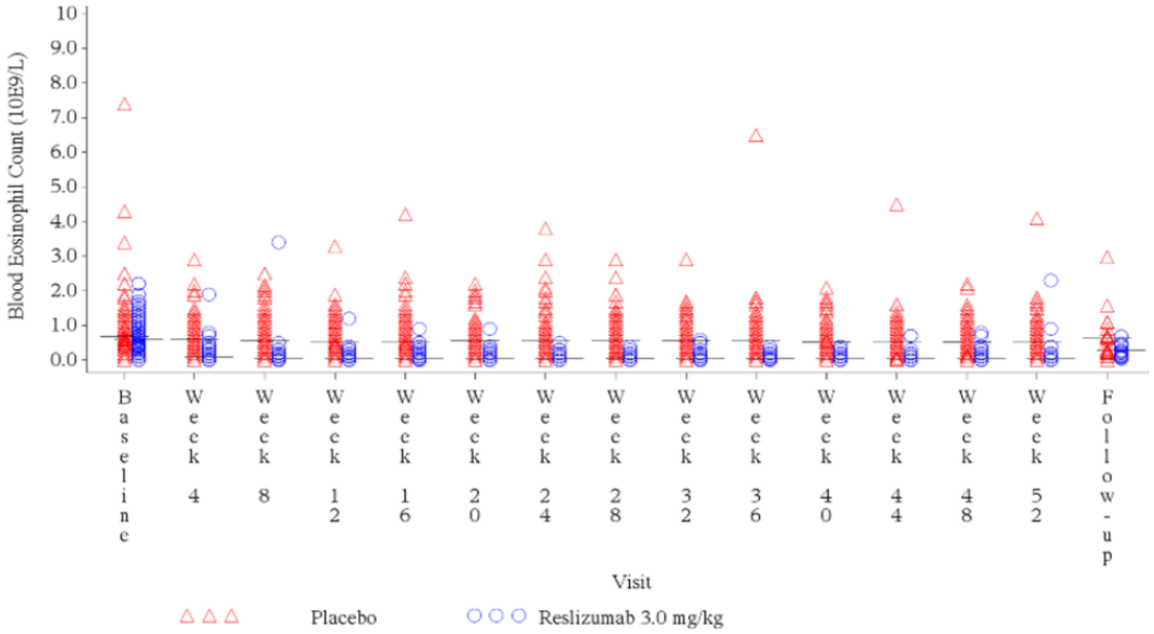
B.3.6.13.2 Change in blood eosinophil count

Reslizumab was associated with a reduction in blood eosinophil counts compared with placebo (Table 36), which was apparent by the first on-treatment assessment at week 4 and sustained for the duration of the study (Figure 27). Blood eosinophils had returned to baseline levels in most patients by the 90-day follow-up visit (90 days after treatment end or early withdrawal) in those patients who did not enrol into the reslizumab open-label safety extension.

Table 36 Change in blood eosinophil count over 16 and 52 weeks

Change in blood eosinophil count (cells/µL)	Placebo (n=232)	Reslizumab (n=232)	Rate ratio (95% CI)	p-value
Week 16	–76	–555	–479 (–519, –439)	<0.0001
Week 52	–76	–565	–489 (–525, –453)	<0.0001
Values shown are LS mean changes over the specified period from baseline. The between-group difference is the absolute reduction in the reslizumab group versus the placebo group Abbreviations: CI; confidence interval, LS; least squares				

Figure 27 Scatter plot of blood eosinophil count over the 52-week treatment period



B.3.6.13.3 Change in ACQ-7 score

The proportion of patients achieving a 0.5-point reduction in ACQ-7 score from baseline to study end was significantly higher in the reslizumab group than in the placebo group (178 [77%] vs 140 [61%]; p=0.0002) (Table 37). Improvements were seen as early as the first on-treatment assessment at week 4, and were sustained through to week 52.

Table 37 Change in ACQ-7 score

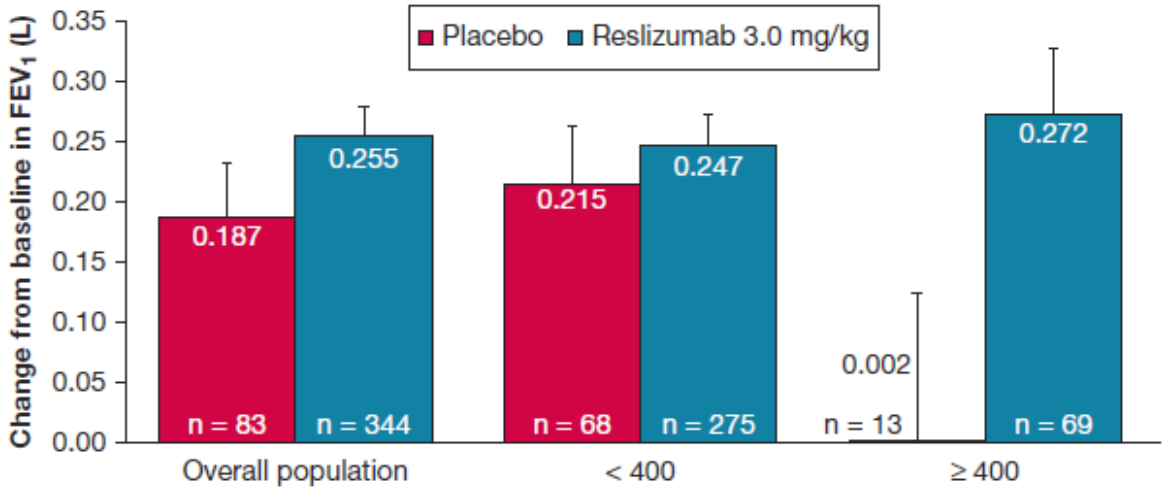
Change in ACQ-7 score	Placebo (n=232)	Reslizumab (n=232)	Rate ratio (95% CI)	p-value
Week 16	–0.66	–0.86	–0.20 (–0.33, –0.07)	0.0032
Week 52	–0.80	–1.04	–0.24 (–0.37, –0.11)	0.0003
Abbreviations: ACQ; Asthma Control Questionnaire, CI; confidence interval				

B.3.6.14 Reslizumab Study 3084: Primary efficacy outcome

B.3.6.14.1 Change from baseline in FEV_1

The primary endpoint was the change in FEV_1 from baseline to week 16. The difference in change in FEV_1 in patients with eosinophils ≥400 cells/μL between the reslizumab (n=69) and placebo (n=13) groups was 270 mL (p=0.04). However, in the overall population, mean FEV_1 change from baseline was not significantly different between reslizumab and placebo groups (p=0.17), nor was it significantly improved in the subgroup of patients with an eosinophil level of <400 cells/μL (p=0.54; Figure 28). Primary efficacy analysis was based on the FAS (all patients receiving ≥1 dose of the study drug).

Figure 28 FEV_1 treatment difference versus placebo by baseline eosinophil count



Data are for FAS.
Abbreviations: FAS; full analysis set, FEV_1; forced expiratory volume in 1 second

Table 38 FEV_1 by baseline eosinophil count

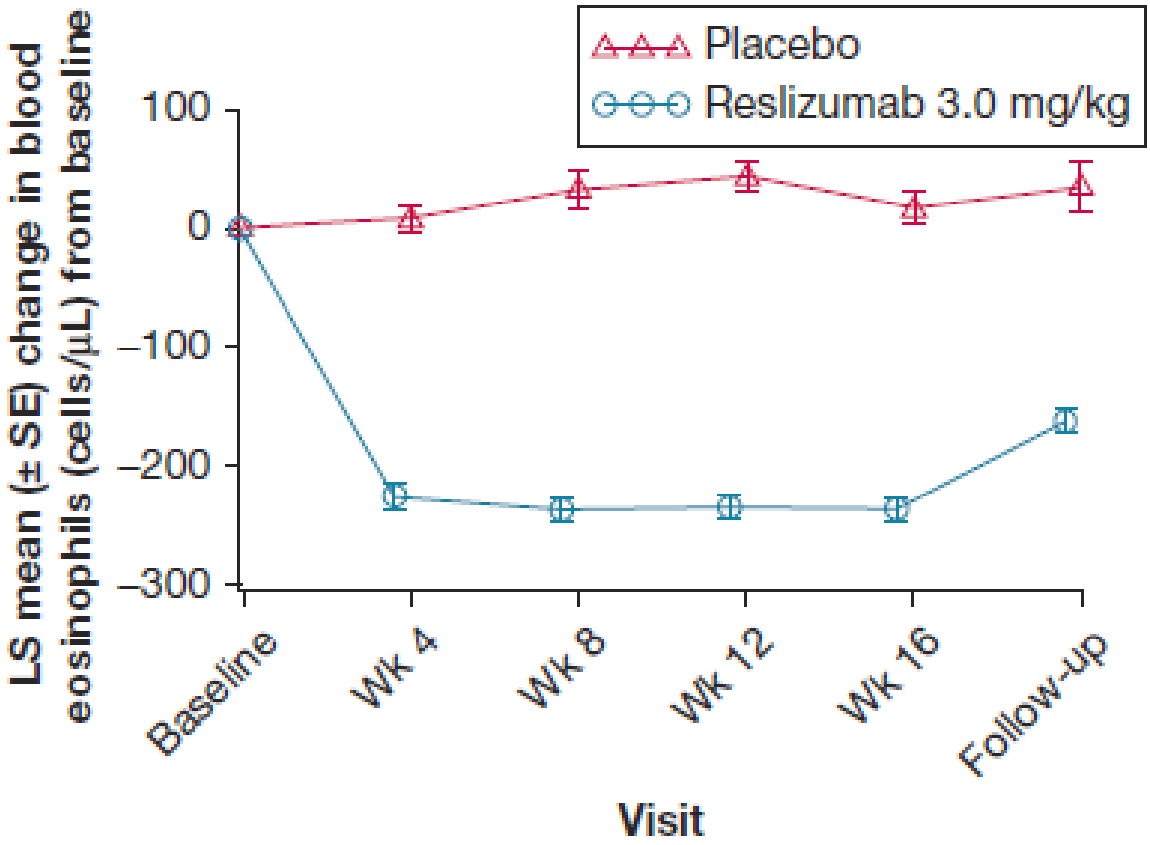
FEV_1, (L)	**Overall population**		**Baseline eosinophils <400 cells/µL**		**Baseline eosinophils ≥400 cells/µL**	
	Placebo (n=97)	*Reslizumab 3.0 mg/kg (n=394)*	*Placebo (n=76)*	*Reslizumab 3.0 mg/kg (n=316)*	*Placebo (n=19)*	*Reslizumab 3.0 mg/kg (n=77)*
Baseline mean ±SE	2.172 ±0.0643	2.098 ±0.0350	2.182 ±0.0746	2.068 ±0.0372	2.153 ±1.392	2.224 ±0.0928
Mean change from baseline ±SE	0.187 ±0.0446	0.255 ±0.0232	0.215 ±0.0484	0.247 ±0.0255	0.002 ±0.1216	0.272 ±0.0557
Treatment effect change ±SE	0.068 ±0.0495		0.033 ±0.0539		0.270 ±0.1320	
95% CI	–0.030, 0.165		–0.073, 0.139		0.008, 0.532	
p-value	0.1719		0.5422		0.0436	
Mean change from baseline expressed as LS mean with associated SE. Abbreviations: CI; confidence interval, LS; least squares, SE; standard error						

B.3.6.15 Reslizumab Study 3084: Secondary outcome measures

B.3.6.15.1 Blood eosinophil count

A marked decrease in blood eosinophils was observed after the first dose of reslizumab compared with placebo and was maintained during the 16 weeks (overall treatment difference, –260 cells/µL; p<0.0001) (Figure 29). Mean blood eosinophil count began to return towards baseline by the follow-up visit (3 months after the end-of-treatment visit and approximately 4 months after last the reslizumab dose).

Figure 29 Blood eosinophils over time by treatment group (all randomised patients)



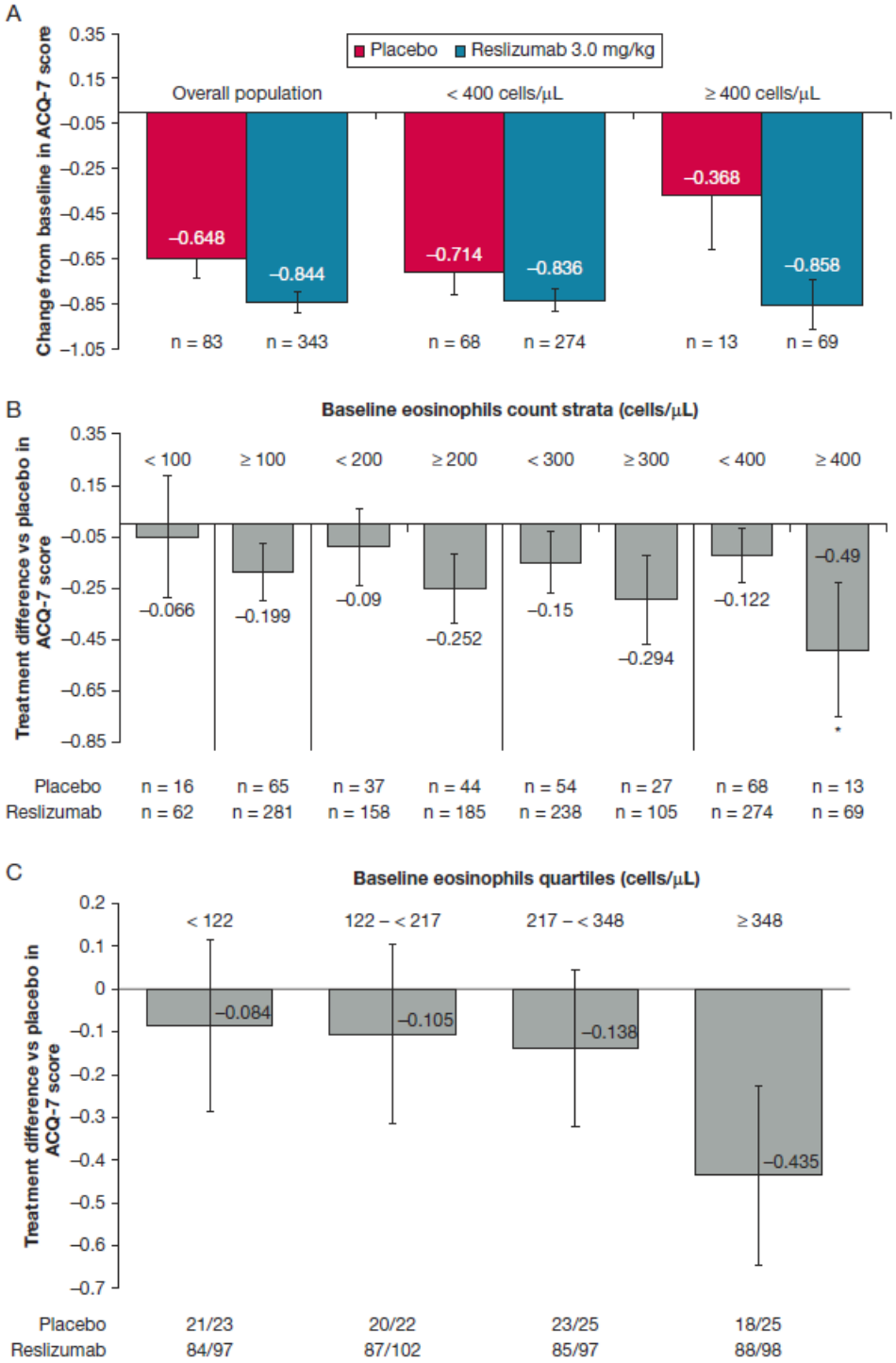
The follow-up visit was conducted 12 weeks ±7 days after the end of treatment at week 16 or early withdrawal.
Abbreviations: LS; least squares, SE; standard error

B.3.6.15.2 ACQ-7 score

The pattern of improvement for ACQ-7 score was consistent with that observed for FEV_1. A greater proportion of patients achieved a clinically meaningful decrease in ACQ-7 score of ≥0.5 at week 16 with reslizumab (71%) versus placebo (57%; p<0.01). The treatment effect in the subgroup of patients with blood eosinophils <400 cells/µL was small. In patients with baseline blood eosinophils ≥400 cells/µL, the increase in ACQ-7 score was more substantial, although not significant (Figure 30)

Figure 30 Change in ACQ-7 scores over 16 weeks, stratified by baseline eosinophil count

(A) ACQ-7 at week 16 by change from baseline in patients with eosinophils ≥400 cells/μL and <400 cells/μL, (B) treatment difference versus placebo by baseline eosinophil strata (FAS) and (C) treatment difference versus placebo by additional baseline eosinophil quartiles.



Abbreviations: ACQ; Asthma Control Questionnaire, FAS; full analysis set

B.3.6.16 Clinical effectiveness results summary for benralizumab

As the NICE guidance for benralizumab (TA565) states that similar efficacy has been accepted between mepolizumab and benralizumab based on analyses provided during this appraisal, it was agreed at the decision problem meeting for this appraisal review that there was no need to present detailed data on all the benralizumab trials and that it was acceptable to assume similar efficacy between these two medicines, particularly as this is further supported by the published indirect treatment comparison (see section B.3.9). However, we have detailed below the primary endpoint data (benralizumab 30 mg every 8 weeks [Q8W], licensed regimen) reported for the three primary studies included in the original NICE submission, TA565, which can be reviewed for further information as necessary.

Reported for the SIROCCO study, benralizumab decreased the annual asthma exacerbation rate by 51% compared with placebo at week 48, with a rate ratio versus placebo of 0.49 (95% CI: 0.37, 0.64; p<0.0001). Overall, 34.8% of patients treated with benralizumab Q8W experienced at least one exacerbation during the study period, compared with 50.6% of patients on placebo. During the CALIMA study, benralizumab decreased the annual asthma exacerbation rate by 28% compared with placebo at week 56, with a rate ratio versus placebo of 0.72 (0.54, 0.95; p=0.018). Overall, 39.7% of patients treated with benralizumab Q8W experienced an exacerbation during the study period compared with 50.8% of patients receiving placebo.

The primary endpoint for the ZONDA study was reduction in OCS use. By study end, the median OCS dose in the benralizumab group had reduced by 75% from baseline, compared with a 25% reduction in OCS dose in the placebo group (p<0.001). This translated to a Hodges-Lehman median treatment difference of 37.5% (95% CI: 20.8, 50.0). The odds of a reduction in OCS dose was 4.12 times higher with benralizumab than with placebo (95% CI: 2.22, 7.63; p<0.001).

Table 39 Primary endpoint results for benralizumab studies: SIROCCO, CALIMA and ZONDA

	Placebo	**Benralizumab 30 mg Q8W**
SIROCCO primary endpoint: Annual asthma exacerbation rate over 48 weeks*		
Number of patients	267	267
Rate estimate (95% CI)	1.33 (1.12, 1.58)	0.65 (0.53, 0.80)
Absolute difference estimate (95% CI)	–	–0.68 (–0.95, –0.42)
Rate ratio vs placebo (95% CI; p-value)	–	0.49 (0.37, 0.64) p<0.0001
CALIMA primary endpoint: Annual asthma exacerbation rate over 56 weeks*		
Number of patients	248	239
Rate estimate (95% CI)	0.93 (0.77, 1.12)	0.66 (0.54, 0.82)
Absolute difference estimate (95% CI)	–	–0.26 (–0.48, –0.04)
Rate ratio vs placebo (95% CI; p-value)	–	0.72 (0.54, 0.95) p=0.0188
ZONDA primary endpoint: Change in median OCS dose over 28 weeks†		
Number of patients	75	73

Median OCS dose at baseline, mg/day (range)	10.0 (7.5–40.0)	10.0 (7.5–40.0)
Median OCS dose at final visit, mg/day (range)	10.0 (0.0–40.0)	5.0 (0.0–30.0)
Median reduction from baseline, % of baseline value (range); p-value	25.0 (–150 to –100)	75.0 (–50–100); p<0.001
*Estimates calculated using a negative binomial model, with adjustment for treatment, region, OCS use at time of randomisation, and previous exacerbations. †The baseline OCS dose was the daily dose at which the patient's asthma was stabilised at randomisation, and the final OCS dose was the final daily dose at week 28. Abbreviations: CI; confidence interval, OCS; oral corticosteroids, Q8W; every 8 weeks		

B.3.7 Subgroup analysis

A subgroup analysis has not been conducted for the purposes of this submission.

B.3.8 Meta-analysis

A meta-analysis has not been conducted for the purposes of this submission.

B.3.9 Indirect and mixed treatment comparisons

No head-to-head trials are available to allow clinical effectiveness comparison of anti-IL-5 treatment options. In the absence of head-to-head data, we provide details of an indirect treatment comparison comparing available anti-IL-5 treatment options, namely mepolizumab, reslizumab and benralizumab.

B.3.9.1 Identification and selection of studies comparing licensed doses of mepolizumab, reslizumab and benralizumab

The indirect comparison was designed to compare the efficacy of licensed doses of mepolizumab, reslizumab and benralizumab in patients with severe eosinophilic asthma, according to baseline blood eosinophil counts. The methods and results of this indirect treatment comparison have previously been published by Busse W, et al.[4] The studies identified for inclusion in the analysis were based in the first instance on a published Cochrane review[40] and then additional searches were completed to identify new studies published after March 2017. The identified studies are shown in Table 40.

The randomised, double-blind, controlled studies considered eligible for inclusion in the indirect treatment comparison were required to meet a predefined Population, Intervention, Comparator, Outcomes, Study Design framework.

- **Population:** patients with severe eosinophilic asthma aged ≥12 years.
- **Comparator:** approved doses or formulations of licensed anti-IL-5 pathway-directed treatments (mepolizumab 100 mg administered SC every 4 weeks, reslizumab 3 mg/kg every 4 weeks, benralizumab 30 mg every 8 weeks [3 × 4 weekly doses followed by 8-weekly dosing]) compared with placebo only.
- **Outcomes:** clinically significant exacerbations, defined as an exacerbation requiring treatment with OCS/systemic corticosteroids (for patients on maintenance OCS, a >2-fold increase in dose was required) or requiring an ED

visit or hospitalisation; exacerbations requiring an ED visit/hospitalisation; ACQ score (any version); and change from baseline pre-bronchodilator FEV_1.

- **Study design:** randomised, double-blind, controlled, with no restrictions on study timeframe or duration.
- The additional search identified two pooled analyses that were used to support the indirect treatment comparison: the first one analysed two benralizumab studies and provided data for patients with baseline blood eosinophil counts of ≥150 cells/μL,[41] while the second analysed two reslizumab studies and provided more details on the endpoint of exacerbations requiring hospitalizations/ED visits.[42]

Table 40 Summary of the trials used to carry out the indirect treatment comparison

References of trial	Mepolizumab	Reslizumab	Benralizumab
MEA115588 [MENSA][8]	✓		
MUSCA[33]	✓		
*NCT00587288[43]		✓	
Study 3081[34]		✓	
Study 3082[35]		✓	
Study 3083[35]		✓	
Study 3084[36]		✓	
SIROCCO[37]			✓
CALIMA[38]			✓
***This is a Phase 2 trial. Full details have not been provided in this submission, as there is Phase 3 data available for reslizumab**.			

B.3.9.2 Methods and outcomes of studies included in the indirect treatment comparison

Prior to treatment comparisons, clinical characteristics of interest were defined so that the varying study populations could be more accurately divided and then compared based on factors that directly impact treatment efficacy.

Baseline blood eosinophil counts were selected because there is evidence to support that blood eosinophil counts influence the efficacy outcomes for the three treatments (more favourable treatment effect estimates are expected in patients with higher baseline blood eosinophil counts).[20,37,43] The randomised, controlled trials for the three anti-IL-5 pathway treatments used different blood eosinophil count inclusion criteria, indicating that subgroup analyses based on the following thresholds (≥150, ≥300 and ≥400 cells/μL) would be most appropriate for this indirect treatment comparison. The study inclusion criteria generated some heterogeneity between the study populations (Table 41).

Table 41 Differences in study inclusion criteria between studies included in the indirect treatment comparison

Characteristic	Mepolizumab	Reslizumab	Benralizumab
Baseline blood eosinophils	≥150 cells/μL at baseline or ≥300 cells/μL in past year	≥400 cells/μL	≥300 cells/μL*
Exacerbation history	≥2 exacerbations in past year	≥1 exacerbation in past year†	≥2 exacerbations in past year
ICS dose	High	Medium-high	High
Maintenance OCS use	Allowed, any dose	Allowed, ≤10 mg prednisolone/day	Allowed, any dose
% predicted FEV_1	<80% (<90% for age <18 years)	Not required	<80% (<90% for age <18 years)
ACQ score	Not required	ACQ-7 ≥1.5	ACQ-6 ≥1.5

*Inclusion criteria for benralizumab studies were wider for blood eosinophil and ICS dose. However, results were reported for the ≥300 cells/μL and high-ICS dose patient population

†Data for the endpoint of exacerbations requiring ED visit/hospitalisation were reported in the reslizumab pooled analysis; patients had ≥2 exacerbations in the past year and GINA Step 4/5 therapy

Abbreviations: ACQ; Asthma Control Questionnaire, ED; emergency department, FEV_1; forced expiratory volume in 1 second, GINA; Global Initiative for Asthma, ICS; inhaled corticosteroids, OCS; oral corticosteroids

Additional subgroups were deemed of clinical interest if they fulfilled the following criteria:

1. Evidence that the characteristic acts as an effect modifier for any of the three treatments;
2. A difference in distribution of characteristics between the included studies across treatments;
3. data are available to perform comparisons.

As a result of this assessment, exacerbation history was also included as a subgroup of interest.

Table 42 Summary of baseline characteristics from the trials used to carry out the indirect treatment comparison

Characteristic	Mepolizumab			
	MEA115588 [MENSA][8]		***MUSCA[33]***	
	Mepolizumab 100 mg SC (N=194)	*Placebo (N=191)*	*Mepolizumab 100 mg SC (N=274)*	*Placebo (N=277)*
Age, years (mean)	51	49	49.8	52.1
Female sex, N (%)	116 (60)	107 (56)	149 (54)	176 (64)
Baseline pre-bronchodilator FEV_1 L, mean (SD) Percent predicted, mean (SD)[§]	 1.73 (0.66) 59.3 (17.5)	 1.86 (0.63) 62.4 (18.1)	 1.8 (0.6) 55.5 (14.4)	 1.7 (0.6) 55.2 (14.6)
ACQ score, mean (SD)	2.26 (1.27)[‖]	2.28 (1.19)[‖]	2.2 (1.1)[‖]	2.2 (1.2)[‖]
Blood eosinophil count, mean cells/µL	290**	320**	300**	350**
Exacerbations in 12 months before screening, mean (SD)	3.8 (2.7)[††]	3.6 (2.80)[††]	2.9 (1.9)	2.7 (1.5)
Patients experiencing ≥1 exacerbation in 12 months before baseline, N (%)	33 (17)[‡‡]	35 (18)[‡‡]	87 (32)[§§]	92 (33)[§§]

Characteristic	Reslizumab									
	NCT00587288[43]		***Study 3081[34]***		***Study 3082[35]***		***Study 3083[35]***		***Study 3084[36]***	
	Reslizumab 3 mg/kg Q4W (N=53)	*Placebo (N=53)*	*Reslizumab 3 mg/kg Q4W (N=106)*	*Placebo (N=105)*	*Reslizumab 3 mg/kg Q4W (N=245)*	*Placebo (N=244)*	*Reslizumab 3 mg/kg Q4W (N=232)*	*Placebo (N=232)*	*Reslizumab 3 mg/kg Q4W (N=398)*	*Placebo (N=98)*
Age, years (mean)*	44.9	45.8	43.0	44.2	49[†]	48[†]	48[†]	48[†]	44.9	45.1

Female sex, N (%)	34 (64)	29 (55)	61 (58)	62 (59)	142 (58)	161 (66)	144 (62)	150 (65)	261 (66)	54 (55)
Baseline pre-bronchodilator FEV_1 L, mean (SD) Percent predicted, mean (SD)[§]	 2.1 (0.60) 66.0 (15.2)	 2.3 (0.75) 69.3 (16.4)	 2.19[‡] 70.4[‡]	 2.22[‡] 71.1[‡]	 1.89 (0.73) 63.6 (18.6)	 1.93 (0.80) 65.0 (19.8)	 2.13 (0.78) 70.4 (21.0)	 2.00 (0.67) 68.0 (18.9)	 2.10[‡] 66.8[‡]	 2.18[‡] 66.5[‡]
ACQ score, mean (SD)	2.8 (0.79)[‖]	2.5 (0.73)[‖]	2.59[‡¶]	2.47[‡¶]	2.66 (0.85)[¶]	2.76 (0.88)[¶]	2.57 (0.89)[¶]	2.61 (0.79)[¶]	2.56[¶]	2.56[¶]
Blood eosinophil count, mean cells/μL	500[†]	500[†]	592	601	696	624	610	688	281	277
Exacerbations in 12 months before screening, mean (SD)	NA	NA	NA	NA	1.9 (1.6)	2.1 (2.3)	1.9 (1.6)	2.0 (1.8)	NA	NA
Patients experiencing ≥1 exacerbation in 12 months before baseline, N (%)	NA	NA	NA (57)	NA (54)	NA	NA	NA	NA	166 (42)	37 (38)

Characteristic	**Benralizumab**			
	***SIROCCO*[37]**		***CALIMA*[38]**	
	Benralizumab 30 mg Q8W (N=267)	*Placebo (N=267)*	*Benralizumab 30 mg Q8W (N=239)*	*Placebo (N=248)*
Age, years (mean)	47.6	48.6	49.6	48.5
Female sex, N (%)	174 (65)	180 (67)	138 (58)	145 (58)
Baseline pre-bronchodilator FEV_1 L, mean (SD) Percent predicted, mean (SD)[§]	 1.66 (0.57) 55.5 (14.6)	 1.65 (0.58) 56.4 (14.6)	 1.76 (0.62) 57.0 (14.2)	 1.82 (0.65) 58.2 (13.9)
ACQ score, mean (SD)	2.81 (0.89)[#]	2.90 (0.95)[#]	2.80 (0.95)[#]	2.75 (0.94)[#]
Blood eosinophil count, mean cells/μL	500[†]	500[†]	500[†]	510[†]

Exacerbations in 12 months before screening, mean (SD)	NA	NA	NA	NA
Patients experiencing ≥1 exacerbation in 12 months before baseline, N (%)	2.8 (1.5)	3.1 (2.0)	2.7 (1.3)	2.8 (1.7)

*Except where otherwise stated

[†]Median reported

[‡]No SD data are available

[§]Spirometric equations used to calculate percent predicted FEV_1 were not provided in the respective publications

[‖]ACQ-5

[¶]ACQ-7

[#]ACQ-6

**Geometric mean reported

[††]Severe exacerbations

[‡‡]Exacerbations requiring hospitalisation

[§§]Exacerbations requiring ED visits/hospitalisations in the 12 months before screening

Abbreviations: ACQ; Asthma Control Questionnaire, ED; emergency department, FEV_1; forced expiratory volume in 1 second, NA; not applicable, Q4W; every 4 weeks, Q8W; every 8 weeks, SC; subcutaneous, SD; standard deviation

Based on the available data, comparative analyses were feasible in the following subgroups:

- 150 cells/μL or greater (mepolizumab and benralizumab studies)
- 300 cells/μL or greater (mepolizumab and benralizumab studies)
- 400 cells/μL or greater (mepolizumab, benralizumab and reslizumab studies)
- Three or more exacerbations in the previous year (mepolizumab and benralizumab [>300 cells/mL] studies)
- Four or more exacerbations in the previous year (mepolizumab, benralizumab [>300 cells/mL] and reslizumab [>400 cells/mL] studies)

Comparisons based on eosinophil thresholds could be performed across all endpoints. However, comparisons based on exacerbation history could only be performed for clinically significant exacerbations. Benralizumab and reslizumab studies excluded patients with ACQ scores <1.5 points at baseline. Therefore, for mepolizumab treatment effects to be comparable, estimates were obtained by using individual patient data excluding patients with ACQ scores <1.5 points at baseline.

Indirect treatment effect estimates were produced using the Bucher method.[42] Inverse variance weighting and DerSimonian and Laird methods were used for fixed and random effects meta-analyses of each treatment versus placebo, respectively.[43] I^2 values, associated 95% CIs and p-values from pairwise comparisons were calculated. I^2 values >50% were considered indicative of heterogeneity between studies, and in such cases random effects estimates were used for that given treatment effect.

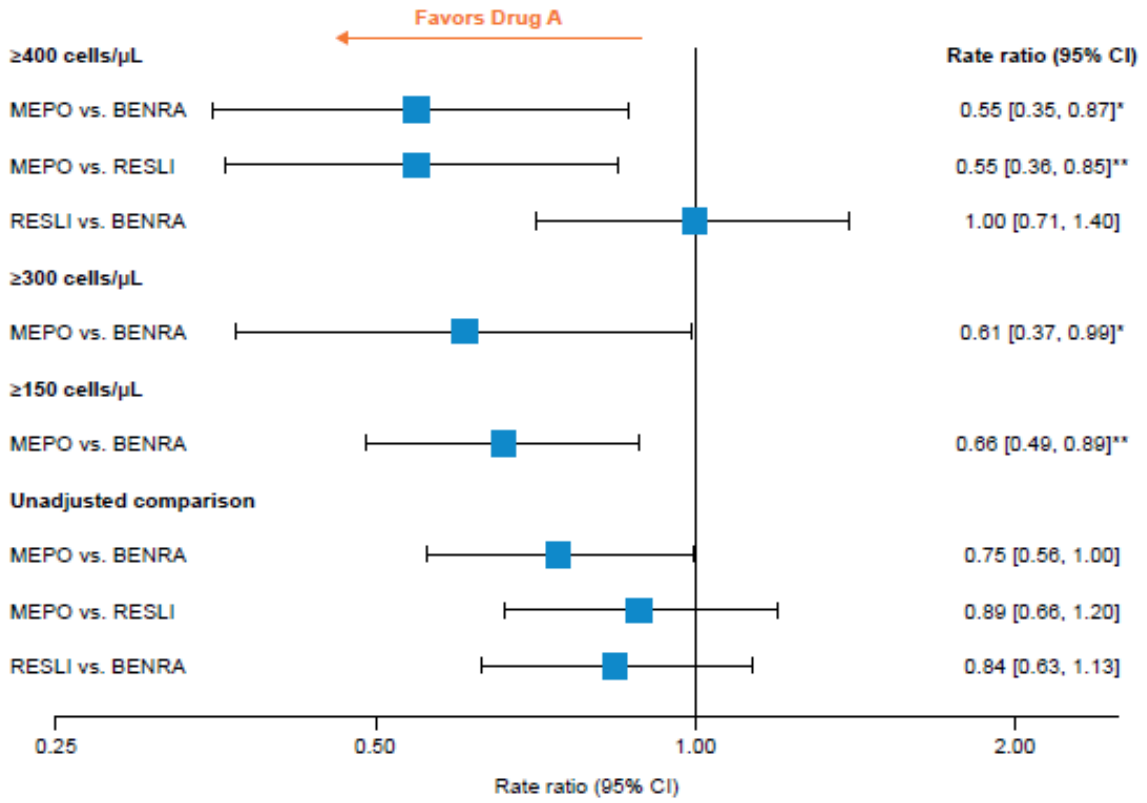
B.3.9.3 Results of the indirect treatment comparison

The mean age of patients was similar across all studies (43.0–52.1 years) and baseline blood eosinophil counts varied, with mean, median and geometric mean values ranging from 277–696 cells/μL across studies.

B.3.9.3.1 Clinically significant exacerbations

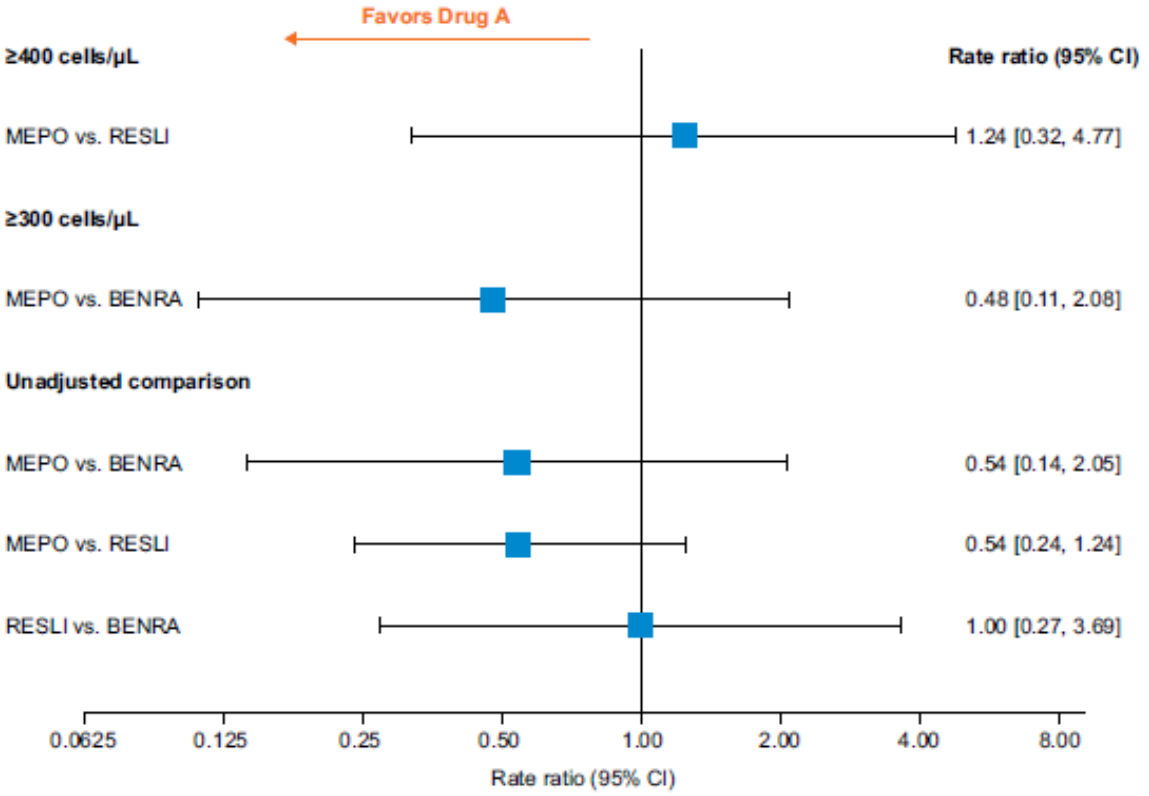
Mepolizumab significantly reduced the rate of clinically significant exacerbations compared with benralizumab (rate ratio: 0.55 [95% CI: 0.35, 0.87]; p=0.011) and reslizumab (rate ratio: 0.55 [95% CI: 0.36, 0.85]; p=0.007) among patients with baseline blood eosinophil counts of 400 cells/μL or greater; there was no difference in exacerbation reduction between reslizumab and benralizumab. In patients with baseline blood eosinophil counts of 150 cells/μL or greater and 300 cells/μL or greater, mepolizumab significantly reduced the rate of clinically significant exacerbations compared with benralizumab (rate ratio: 0.66 [95% CI: 0.49, 0.89]; p=0.006 and 0.61 [95% CI: 0.37, 0.99]; p=0.047, respectively).

Figure 31 Comparison of the rate of clinically significant exacerbations by baseline blood eosinophil count subgroups and in the ITT population



*p<0.05
**p<0.01
Comparisons are presented as drug A versus drug B. For exacerbations requiring ED visits/hospitalisations, no significant differences were observed between any two treatments in any subgroup assessed
Abbreviations: BENRA; benralizumab, CI; confidence interval, ED; emergency department, ITT; intention-to-treat, MEPO; mepolizumab, RESLI; reslizumab

Figure 32 Comparison of the rate of exacerbations requiring ED visits/hospitalisations by baseline blood eosinophil count subgroup and in the ITT population. Comparisons are presented as drug A versus drug B



Not all comparisons were possible at each blood eosinophil count threshold because of a lack of data from included studies. I^2 values: ≥400 cells/mL, 12% (MEPO vs PBO) and NA (RESLI vs PBO); ≥300 cells/mL, 0% (MEPO vs PBO) and 86% (BENRA vs PBO); unadjusted comparison, 0% (MEPO vs PBO), 86% (BENRA vs PBO), and 0% (RESLI vs PBO). BENRA, 30 mg of benralizumab Q8W; MEPO, 100 mg of mepolizumab administered subcutaneously; RESLI, 3 mg/kg reslizumab
Abbreviations: BENRA; benralizumab, ED; emergency department, ITT; intention-to-treat, NA; not applicable, Q8W; every 8 weeks, MEPO; mepolizumab, RESLI; reslizumab

Among patients with baseline blood eosinophil counts of 400 cells/µL or greater, for the endpoint of clinically significant exacerbations, mepolizumab ranked first (p=0.997), followed by reslizumab (p=0.504) and benralizumab (p=0.499). However, for exacerbations requiring ED visit/hospitalisation, reslizumab ranked higher than mepolizumab (p=0.810 vs 0.681).

Table 43 Summary of treatment ranks and p-values for mepolizumab, reslizumab and benralizumab for each endpoint by baseline blood eosinophil count subgroup and in the ITT population

	Treatment rank (p-value)		
	1	**2**	**3**
Clinically significant exacerbations			
≥400 cells/μL	MEPO (0.997)	RESLI (0.504)	BENRA (0.499)
≥300 cells/μL	MEPO (0.998)	BENRA (0.510)	–
≥150 cells/μL	MEPO (0.998)	BENRA* (0.502)	–
Unadjusted comparison	MEPO (0.917)	RESLI (0.699)	BENRA (0.384)
Exacerbations requiring ED visits/hospitalisations			
≥400 cells/μL	RESLI† (0.810)	MEPO (0.681)	–
≥300 cells/μL	MEPO (0.956)	BENRA (0.455)	–
Unadjusted comparison	MEPO (0.952)	RESLI (0.483)	BENRA (0.477)
Asthma control score			
≥400 cells/μL	MEPO (0.995)	BENRA (0.552)	RESLI (0.453)
≥300 cells/μL	MEPO (0.991)	BENRA (0.501)	–
≥150 cells/μL	MEPO (0.999)	BENRA* (0.500)	–
Unadjusted comparison	MEPO (0.970)	RESLI (0.519)	BENRA (0.511)
Pre-bronchodilator FEV_1			
≥400 cells/μL	BENRA (0.915)	MEPO (0.697)	RESLI (0.389)
≥300 cells/μL	MEPO (0.910)	BENRA (0.590)	–
≥150 cells/μL	MEPO (0.808)	BENRA* (0.692)	–
Unadjusted comparison	BENRA (0.744)	RESLI (0.716)	MEPO (0.540)

*Data for the 150 cells/μL or greater subgroup were reported in the published benralizumab pooled analysis only

†Data for the end point of exacerbations requiring ED visits/hospitalisations were reported in the published reslizumab pooled analysis. Patients had two or more exacerbations in the past year and GINA Step 4/5 therapy

Abbreviations: BENRA; benralizumab, ED; emergency department, GINA; Global Initiative for Asthma, ITT; intention-to-treat, MEPO; mepolizumab, RESLI; reslizumab

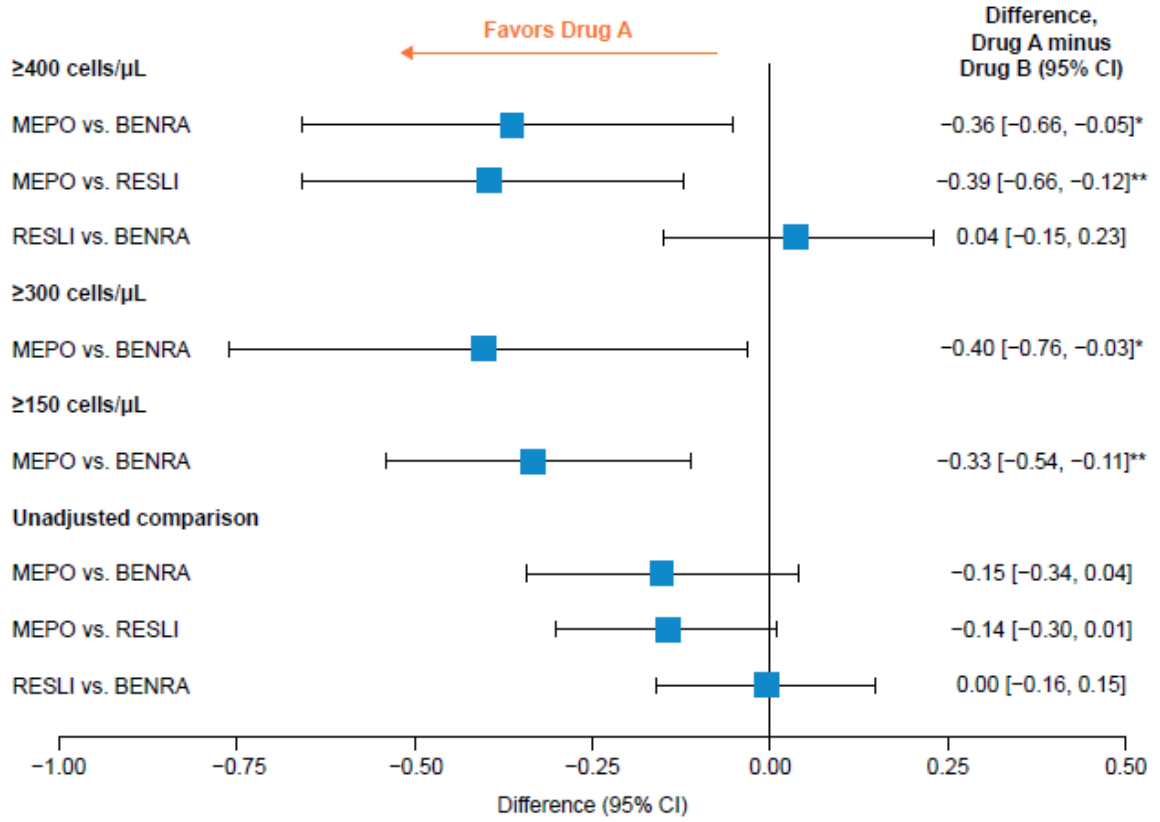
Results for the additional subgroup analyses of mepolizumab and benralizumab conducted among patients with blood eosinophil counts of 300 cells/μL or greater, further stratified by exacerbation history, were in line with results observed for all patients with blood eosinophil counts of 300 cells/μL or greater.

B.3.9.3.2 Patient-reported asthma control

In patients with baseline blood eosinophil counts of 400 cells/μL or greater, mepolizumab was associated with significant improvements in change from baseline in ACQ scores compared with benralizumab (difference: –0.36 [95% CI: –0.66, –0.05]; p=0.023) and reslizumab (difference: –0.39 [95% CI: –0.66, –0.12]; p=0.004). There was no significant difference in change from baseline in ACQ score between reslizumab and benralizumab. In subgroups with baseline blood eosinophil counts of 150 cells/μL or greater and 300 cells/μL or greater, mepolizumab treatment was associated with significant improvements in change from baseline in ACQ scores

compared with benralizumab (difference: –0.33 [95% CI: –0.54, –0.11; p=0.003] and –0.40 [95% CI: –0.76, –0.03; p=0.035], respectively).

Figure 33 Comparison of the change from baseline in ACQ score by baseline blood eosinophil count subgroups and in the ITT population



*p<0.05
**p<0.01
Comparisons are presented as drug A versus drug B. Not all comparisons were possible at each blood eosinophil count threshold because of a lack of data from included studies. I^2 values: ≥400 cells/mL, 28% (MEPO vs PBO), NA (BENRA vs PBO), and 0% (RESLI vs PBO); ≥300 cells/mL, 60% (MEPO vs PBO) and 0% (BENRA vs PBO); 150 cells/mL or greater, 0% (MEPO vs PBO) and NA (BENRA vs PBO); unadjusted comparison, 0% (MEPO vs PBO), 0% (BENRA vs PBO), and 0% (RESLI vs PBO). BENRA, 30 mg of benralizumab Q8W; MEPO, 100 mg of mepolizumab administered subcutaneously; RESLI, 3 mg/kg reslizumab
Abbreviations: ACQ; Asthma Control Questionnaire, BENRA; benralizumab, CI; confidence interval, ITT; intention-to-treat, NA; not applicable, Q8W; every 8 weeks, MEPO; mepolizumab, RESLI; reslizumab

For patient-reported asthma control, among patients with baseline blood eosinophil counts of 400 cells/µL or greater, mepolizumab ranked first (p=0.995), followed by benralizumab (p=0.552) and reslizumab (p=0.453) (Table 43).

B.3.9.3.3 Lung function

At all eosinophil count thresholds, there were no significant differences in change from baseline in pre-bronchodilator FEV_1 between mepolizumab and benralizumab. Additionally, among patients with baseline blood eosinophil counts of 400 cells/µL or greater, no significant differences were observed between mepolizumab and

reslizumab. However, benralizumab was associated with a significant improvement in change from baseline in FEV_1 compared with reslizumab (difference: 0.11 [95% CI: 0.01, 0.20; p=0.025]). For pre-bronchodilator FEV_1, among patients with baseline blood eosinophil counts of 400 cells/μL or greater, benralizumab ranked highest (p=0.915), followed by mepolizumab (p=0.697) and reslizumab (p=0.389). Mepolizumab ranked higher than benralizumab in patients with baseline blood eosinophil counts of 300 cells/μL or greater (p=0.910 vs 0.590) and 150 cells/μL or greater (p=0.808 vs 0.692) (Table 43).

B.3.9.4 Results of the statistical assessment of heterogeneity

I^2 values of greater than 50% were considered indicative of heterogeneity between studies, and in such cases random effects estimates were used for that given treatment effect.

There was no evidence of heterogeneity among the mepolizumab and reslizumab studies. A high degree of heterogeneity was observed among benralizumab studies. However, these studies were of comparable length, and therefore the observed heterogeneity is unlikely to be due to study duration. In addition, one published meta-analysis of mepolizumab studies, which combined data from two studies of 32 (MENSA) and 52 (DREAM) weeks' duration, reported consistent findings across studies within all investigated subgroups.[46]

Table 44 Estimates of heterogeneity across studies for exacerbations

Treatment	Included studies	Range of duration (weeks)	I^2 (ITT)
Mepolizumab	MENSA, MUSCA	24–32	0%
Reslizumab	Studies 3082 and 3083*	52	0%
Benralizumab	SIROCCO, CALIMA	48–56	73–86%
*Other reslizumab studies were not included in this analysis because they did not have clinically significant exacerbations or exacerbations requiring ED visit/hospitalisation as endpoints Abbreviations: ED; emergency department, ITT; intention-to-treat			

Evidence regarding the time dependency of the treatment difference in change from baseline ACQ score was consistent across the three treatments. There was no evidence of heterogeneity among the mepolizumab and reslizumab studies. As a result of this assessment, it was found unlikely that study duration would have a large effect on comparisons when using estimates of treatment difference in the change from baseline ACQ score for the included treatments. Based on benralizumab and reslizumab data, the likely effect would be that results from studies with longer follow-up (up to 56 weeks) would yield slightly more favourable treatment differences versus shorter studies. Therefore, further adjustment for study duration was not deemed necessary.

Table 45 Estimates of heterogeneity across studies for ACQ score

Treatment	Included studies	Range of duration (weeks)	I^2 (ITT)
Mepolizumab	MENSA, MUSCA	24–32	0%
Reslizumab	Studies 3082 and 3083, NCT00587288, NCT01508936, NCT01270464	15–52	0%
Benralizumab	SIROCCO, CALIMA	48–56	0%
Abbreviations: ACQ; Asthma Control Questionnaire, ITT; intention-to-treat			

Evidence regarding the time dependency of the treatment difference in change from baseline pre-bronchodilator FEV_1 score was consistent across the three treatments. There was no evidence of heterogeneity among the mepolizumab and reslizumab studies. As a result of this assessment, it was found unlikely that study duration would have a large effect on comparisons when using estimates of treatment difference in the change from baseline FEV_1 for the included treatments. Therefore, further adjustment for study duration was not deemed necessary.

Table 46 Estimates of heterogeneity across studies for pre-bronchodilator FEV_1

Treatment	Included studies	Range of duration (weeks)	I^2 (ITT)
Mepolizumab	MENSA, MUSCA	24–32	0%
Reslizumab	Study 3082 and 3083, NCT00587288, NCT01508936, NCT01270464	15–52	13%
Benralizumab	SIROCCO, CALIMA	48–56	0%
Abbreviations: FEV_1; forced expiratory volume in 1 second, ITT; intention-to-treat			

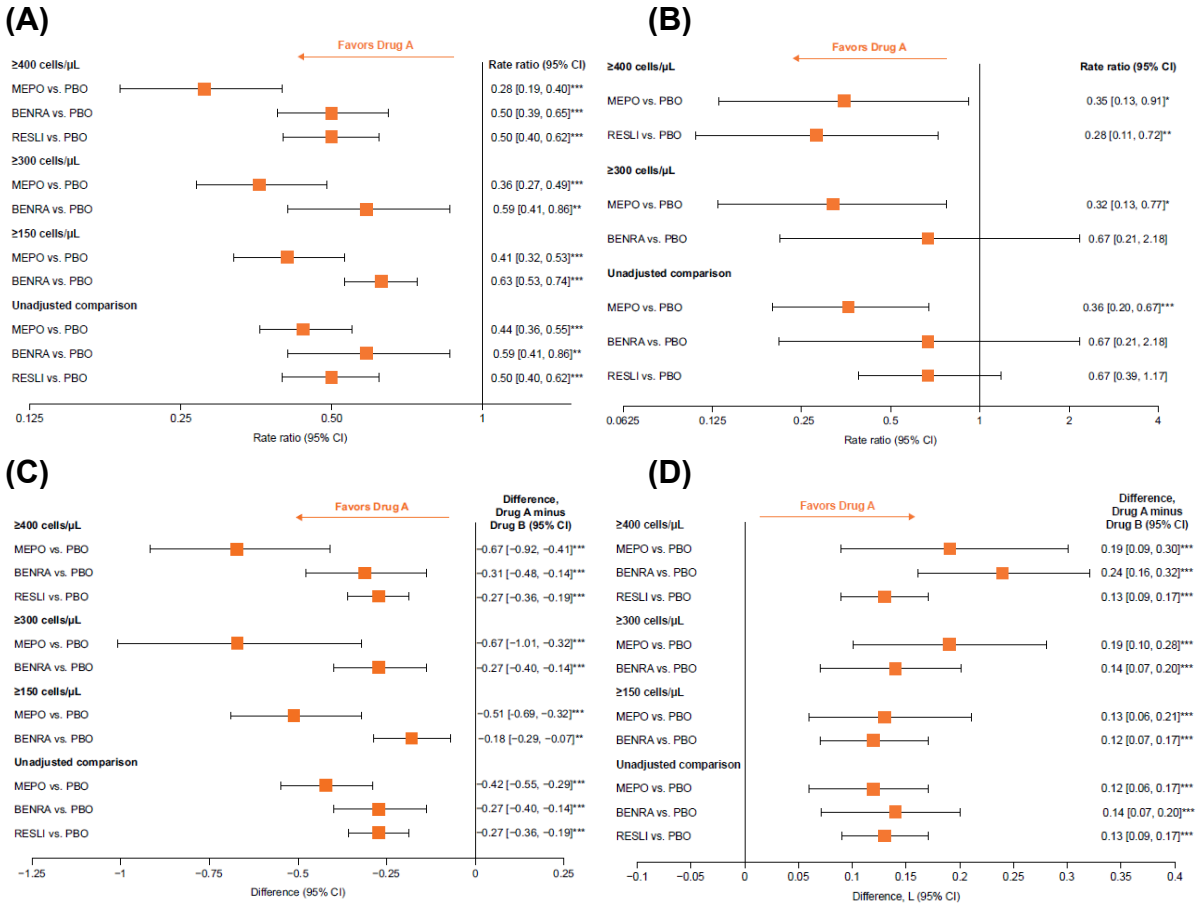
B.3.9.5 Sensitivity analyses

An unadjusted comparison was also performed as a sensitivity analysis for the indirect treatment comparison, in which the ITT populations for all treatments, uncontrolled for baseline blood eosinophil counts or ACQ scores, were used to compare the effect of treatment on the four endpoints.

Compared with placebo, all treatments resulted in significant improvements in the rate of clinically significant exacerbations and changes from baseline in ACQ score and pre-bronchodilator FEV_1. Additionally, as seen in the analysis by blood eosinophil count threshold, mepolizumab significantly reduced the rate of exacerbations requiring ED visits/hospitalisations compared with placebo (see Figure 34).

Figure 34 Treatment comparison with placebo in baseline blood eosinophil count subgroups and the ITT population

(A) rate of clinically significant exacerbations, (B) rate of exacerbations requiring ED visits/hospitalisations, (C) ACQ score and (D) pre-bronchodilator FEV_1 (litres).



*p<0.05
**p<0.01
***p<0.001
Comparisons are presented as drug versus placebo.
Abbreviations: ACQ; Asthma Control Questionnaire, BENRA; benralizumab, CI; confidence interval, ED; emergency department, FEV_1; forced expiratory volume in 1 second, ITT; intention-to-treat, MEPO; mepolizumab, RESLI; reslizumab

In the indirect treatment comparison, no significant differences were observed between any two treatments for any endpoint when using the ITT population (Figure 34).

B.3.9.6 Considerations for review of the indirect evidence comparison

This indirect comparison of the three available anti-IL-5 pathway-directed therapies focused on the licensed formulations of each treatment and clinical endpoints that are common across the trials, taking baseline blood eosinophil counts and ACQ scores into consideration.

Mepolizumab significantly reduced the rate of clinically significant exacerbations by 34% to 45% compared with benralizumab across all baseline blood eosinophil count thresholds, and by 45% compared with reslizumab in the 400 cells/µL or greater

subgroup. Furthermore, mepolizumab was associated with significant improvements in patient-reported asthma control, as assessed by ACQ score, compared with reslizumab and benralizumab in the 400 cells/μL or greater subgroup, and benralizumab in the 150 cells/μL or greater and 300 cells/μL or greater subgroups. A significant improvement in lung function of 110 mL (as assessed by change from baseline in pre-bronchodilator FEV_1) was observed for benralizumab versus reslizumab in patients with baseline blood eosinophil counts of 400 cells/μL or greater. Of note, when treatment comparisons used the ITT populations and did not take into account differences in baseline blood eosinophil count or ACQ score, there were no significant differences among the three treatments. Therefore, accounting for baseline characteristics improved the accuracy of the comparative efficacy of the treatments.

The anti-IL-5 pathway-directed treatments included in this analysis not only differ with respect to their clinical efficacy but also their dosing regimens and possible mechanisms of action. Mepolizumab and reslizumab are anti-IL-5 antibodies, whereas benralizumab is an anti-IL-5 receptor antibody, and the comparison included only the licensed formulations. Comparisons were carried out on patient populations grouped by baseline blood eosinophil count, which is known to influence treatment effect,[20,35,37] and matched according to baseline ACQ score (and in one analysis, exacerbation history), an approach that should allow like-for-like comparisons between treatments. However, the included studies were conducted in different cohorts of patients, different regions over different periods of time and within different healthcare delivery systems. As such, the definition of standard of care will have differed between the included trials, which might have influenced the observed treatment effects, although there is considerable overlap between the different study populations, particularly after the inclusion criteria for blood eosinophil counts and ACQ scores were matched.

The variation in study duration, ranging from 15 to 56 weeks, might have affected treatment comparisons, although there was no evidence of heterogeneity when combining studies of different durations. Despite the change from baseline in each treatment changing through time, the treatment differences (between treatment and placebo) remained consistent from approximately 16 weeks onward in the individual studies, meaning that differences in change from baseline ACQ score and FEV_1 reported from 15 weeks and up to 56 weeks could be compared without further correction. The effect measures used in this analysis (e.g. rate ratio for exacerbations rather than dichotomous outcomes, such as percentage of patients with >1 exacerbation) were also appropriate for combining results from studies of different durations. Therefore, the bias potentially caused by variations in study duration is likely to be small.

A further limitation of the analysis was that the patient populations from the reslizumab studies could not be closely matched with regard to their exacerbation history or ICS use. Closer matching of exacerbation history is of particular importance given the effect of exacerbation history on treatment efficacy. Nonetheless, for the endpoint of exacerbations requiring ED visits/hospitalisations, we were able to match patient subgroups by the presence of two or more historic exacerbations and the use of Global Initiative for Asthma (GINA) Step 4/5 therapy.

Slight variation in the definition of clinically significant exacerbations also existed between studies, and it was not possible to conduct a meta-regression analysis

adjusting for within- and between-study variation in blood eosinophil counts or other baseline covariates because of the small number of available studies and the inconsistency of data reporting between studies (e.g. geometric mean blood eosinophil counts vs non-geometric means). Additionally, the studies used different versions of the ACQ (ACQ-7 in the reslizumab trials, ACQ-6 in the benralizumab trials and ACQ-5 in the mepolizumab trials). However, validation studies have been published showing that all ACQ versions have similar psychometric properties and produce similar results.[47,48] Finally, assessments of lung function were based on FEV_1 in litres because percent-predicted FEV_1 was not available for the majority of the benralizumab or reslizumab studies, meaning the analysis does not account for potential differences in baseline lung function.

B.3.10 Adverse reactions

Indirect treatment comparisons that have revised evidence pertaining to the safety of mepolizumab and reslizumab have reported no significant differences in the adverse event profiles for these two treatments.[40,49] The Cochrane review did note that there was a question to be answered for benralizumab with regards to adverse events significant enough to lead to discontinuation of treatment but otherwise concluded there was no excess of serious adverse events.[40] Full summaries of the adverse event profiles were reported as part of the respective single technology appraisals for mepolizumab (TA431), reslizumab (TA479) and benralizumab (TA565). The reported adverse event profiles are provided below for each of the mepolizumab and reslizumab trials detailed in section B.3.2.

More information on safety evaluations from long-term studies of mepolizumab is provided in Appendix F.

B.3.10.1 Mepolizumab reported adverse event profile

Across the four randomised, placebo-controlled trials included in this submission (MEA112997 [DREAM],[20] MEA115588 [MENSA],[8] MEA115575 [SIRIUS],[32] MUSCA[33]), mepolizumab was generally well tolerated. The combined adverse event profile reported for the MEA112997 [DREAM], MEA115588 [MENSA] and MEA115575 [SIRIUS] studies is detailed in Table 47. The incidence of adverse events across the studies was similar for the placebo group (82%) compared with the mepolizumab 100 mg SC group (79%), and the mepolizumab 75 mg IV group (83%).[1] A similar pattern was reported for the MUSCA study, with an adverse event incidence rate of 74% for the placebo group and 70% for the mepolizumab 100 mg SC group.[33]

The most common adverse events recorded by patients receiving mepolizumab during the studies were headache, nasopharyngitis, bronchitis and sinusitis. Injection site reactions were reported in 3–12% of patients receiving mepolizumab, compared with 1–6% of patients receiving placebo.[8,20,32,33] These events were all non-serious and mild to moderate in intensity, and the majority resolved within a few days. The common symptoms reported with these events included pain, erythema, swelling, itching and a burning sensation. Two patients withdrew due to injection site reactions.[1]

Systemic reactions were reported in one study (MEA115575 [SIRIUS]) for 3/66 of patients receiving placebo and 4/69 of patients receiving mepolizumab,[32] and in

another study (MUSCA) for 2/278 patients receiving placebo and 2/273 patients receiving mepolizumab.[33] Hypersensitivity deemed possibly related to mepolizumab was reported by 2% of patients receiving placebo, no patients receiving 75 mg mepolizumab, <1% of patients receiving 250 mg mepolizumab and 1% receiving 750 mg mepolizumab in the MEA112997 [DREAM] study.[20] Two studies reported immunogenicity testing for anti-mepolizumab antibodies. In study MEA115588, positive anti-mepolizumab antibodies were reported for 4% of patients receiving IV mepolizumab, 5% receiving SC mepolizumab and 2% in the placebo group. None had neutralising antibodies.[8] In study MEA115575, post-baseline testing revealed five patients had non-neutralising antibodies at low titre and one patient had neutralising antibodies after the first dose of mepolizumab (titre, 160), increasing to 640 titre at week 32.[32]

Table 47 Summary of most frequent on-treatment adverse events reported by 3% or more of subjects in any treatment group across three mepolizumab studies (MEA112997 [DREAM], MEA115588 [MENSA], MEA115575 [SIRIUS])[1]

Event	Treatment	N	Number (%) with event		Adjusted cumulative proportion	Relative risk	(95% CI)*
Eczema	Placebo	412	2	0.50%	0.50%		
	All doses	915	23	2.50%	2.60%	5.34	(1.25, 22.78)
Nasal congestion	Placebo	412	4	1.00%	1.00%		
	All doses	915	24	2.60%	2.50%	2.62	(0.89, 7.72)
Dyspnoea	Placebo	412	4	1.00%	1.10%		
	All doses	915	23	2.50%	2.30%	2.2	(0.78, 6.20)
Rhinitis allergic	Placebo	412	7	1.70%	1.70%		
	All doses	915	27	3.00%	2.80%	1.64	(0.70, 3.85)
Urinary tract infection	Placebo	412	9	2.20%	2.10%		
	All doses	915	32	3.50%	3.40%	1.63	(0.77, 3.47)
Pharyngitis	Placebo	412	8	1.90%	2.00%		
	All doses	915	25	2.70%	2.70%	1.34	(0.61, 2.97)
Abdominal pain upper	Placebo	412	8	1.90%	2.00%		
	All doses	915	24	2.60%	2.60%	1.32	(0.59, 2.95)
Pyrexia	Placebo	412	9	2.20%	1.90%		
	All doses	915	22	2.40%	2.50%	1.29	(0.57, 2.94)
Back pain	Placebo	412	20	4.90%	5.00%		
	All doses	915	60	6.60%	6.30%	1.26	(0.77, 2.06)
Infusion related reaction	Placebo	412	11	2.70%	2.90%		
	All doses	915	40	4.40%	3.70%	1.24	(0.65, 2.38)
Injection site reaction	Placebo	412	13	3.20%	3.20%		
	All doses	915	31	3.40%	3.80%	1.2	(0.64, 2.23)
Headache	Placebo	412	74	18.00%	17.80%		
	All doses	915	195	21.30%	21.30%	1.2	(0.94, 1.53)
Gastroenteritis	Placebo	412	9	2.20%	2.30%		
	All doses	915	24	2.60%	2.70%	1.2	(0.57, 2.52)
Lower respiratory tract	Placebo	412	10	2.40%	2.40%		
	All doses	915	25	2.70%	2.80%	1.14	(0.55, 2.37)

Event	Treatment	N	Number (%) with event		Adjusted cumulative proportion	Relative risk	(95% CI)*
Influenza	Placebo	412	15	3.60%	3.80%		
	All doses	915	37	4.00%	4.00%	1.06	(0.59, 1.89)
Fatigue	Placebo	412	17	4.10%	4.00%		
	All doses	915	35	3.80%	4.10%	1.04	(0.59, 1.84)
Naso-pharyngitis	Placebo	412	80	19.40%	19.40%		
	All doses	915	184	20.10%	19.80%	1.02	(0.80, 1.30)
Arthralgia	Placebo	412	23	5.60%	5.60%		
	All doses	915	50	5.50%	5.60%	0.99	(0.61, 1.61)
Rhinitis	Placebo	412	12	2.90%	3.00%		
	All doses	915	25	2.70%	2.90%	0.96	(0.50, 1.84)
Hypertension	Placebo	412	12	2.90%	3.00%		
	All doses	915	28	3.10%	2.90%	0.95	(0.49, 1.85)
Pain in extremity	Placebo	412	16	3.90%	3.90%		
	All doses	915	32	3.50%	3.60%	0.9	(0.50, 1.62)
Dizziness	Placebo	412	13	3.20%	3.00%		
	All doses	915	25	2.70%	2.70%	0.9	(0.45, 1.80)
Upper respiratory tract	Placebo	412	47	11.40%	11.50%		
	All doses	915	96	10.50%	10.30%	0.9	(0.64, 1.25)
Bronchitis	Placebo	412	39	9.50%	9.50%		
	All doses	915	73	8.00%	7.90%	0.83	(0.57, 1.21)
Sinusitis	Placebo	412	40	9.70%	9.80%		
	All doses	915	68	7.40%	7.60%	0.78	(0.54, 1.13)
Oropharyngeal pain	Placebo	412	27	6.60%	6.40%		
	All doses	915	45	4.90%	5.00%	0.77	(0.48, 1.24)
Nausea	Placebo	412	17	4.10%	3.80%		
	All doses	915	26	2.80%	3.00%	0.77	(0.41, 1.44)
Cough	Placebo	412	21	5.10%	5.30%		
	All doses	915	41	4.50%	4.10%	0.77	(0.46, 1.29)
Hyper-sensitivity	Placebo	412	11	2.70%	2.60%		
	All doses	915	18	2.00%	2.00%	0.76	(0.35, 1.64)
Myalgia	Placebo	412	12	2.90%	3.00%		
	All doses	915	19	2.10%	2.10%	0.69	(0.34, 1.41)
Asthma	Placebo	412	61	14.80%	14.90%		
	All doses	915	89	9.70%	9.10%	0.61	(0.45, 0.84)
Oedema peripheral	Placebo	412	13	3.20%	3.20%		
	All doses	915	14	1.50%	1.70%	0.52	(0.25, 1.07)
Diarrhoea	Placebo	412	19	4.60%	4.60%		
	All doses	915	21	2.30%	2.20%	0.47	(0.25, 0.88)

*Adjusted using Cochran–Mantel–Haenszel weights; calculated using the Cochran–Mantel–Haenszel method
Abbreviation: CI; confidence interval

All other relative risks were less than 2. Of the 33 events reported by 3% or more of patients, 17 were reported more frequently with mepolizumab and 16 were reported more frequently with placebo.

B.3.10.1.1 Mepolizumab drug-related adverse events

The incidence of drug-related adverse events across three included studies (MEA112997 [DREAM], MEA115588 [MENSA], MEA115575 [SIRIUS]) was 16% in the placebo group compared with 23% in the mepolizumab 100 mg SC group and 18% in the mepolizumab 75 mg IV group (Table 48). The incidence of drug-related adverse events was similar for the other mepolizumab treatment groups. The most frequently reported drug-related adverse events in the placebo and mepolizumab 100 mg SC and 75 mg IV groups were headache (2%, 5% and 3%, respectively) and injection site reaction (3%, 6% and 2%, respectively). Similar results were also observed in the Phase 3b MUSCA study.

Table 48 Most frequent (≥5 patients across treatment groups) drug-related adverse events (safety population)

Drug-related adverse event* (preferred term)†	**Number (%) of patients**					
	Placebo N=412	***Mepolizumab***				
		100 SC N=263	*75 IV N=344*	*250 IV N=152*	*750 IV N=156*	*All doses N=915*
Any drug-related event	67 (16)	60 (23)	61 (18)	29 (19)	33 (21)	183 (20)
Infusion-related reaction	11 (3)	0	8 (2)	12 (8)	19 (12)	39 (4)
Headache	10 (2)	13 (5)	11 (3)	6 (4)	5 (3)	35 (4)
Injection site reaction	12 (3)	17 (6)	8 (2)	0	0	25 (3)
Fatigue	5 (1)	5 (2)	4 (1)	2 (1)	0	11 (1)
Hypersensitivity	6 (1)	3 (1)	2 (<1)	1 (<1)	2 (1)	8 (<1)
Nausea	7 (2)	3 (1)	0	2 (1)	0	5 (<1)
Arthralgia	2 (<1)	2 (<1)	2 (<1)	1 (<1)	2 (1)	7 (<1)
Dizziness	1 (<1)	4 (2)	0	1 (<1)	1 (<1)	6 (<1)
Myalgia	2 (<1)	2 (<1)	1 (<1)	1 (<1)	1 (<1)	5 (<1)
Oedema peripheral	3 (<1)	0	3 (<1)	0	0	3 (<1)
Hypertension	3 (<1)	0	1 (<1)	2 (1)	0	3 (<1)
Injection-related reaction	3 (<1)	3 (1)	0	0	0	3 (<1)
Migraine	1 (<1)	2 (<1)	0	0	2 (1)	4 (<1)
Vomiting	2 (<1)	1 (<1)	1 (<1)	1 (<1)	0	3 (<1)
Exposure adjusted‡						
Drug-related adverse event (preferred term)	*Placebo Pt years = 284*	***Mepolizumab***				
		100 SC Pt years = 147	*75 IV Pt years = 254*	*250 IV Pt years = 142*	*750 IV Pt years = 144*	*All doses Pt years = 687*
Infusion-related reaction	73.9	0	55.1	239.1	383.3	149.8
Injection site reaction	95.1	183.1	39.3	0	0	53.8
Headache	52.8	162.7	82.6	56.3	97.6	97.5
Fatigue	17.6	47.5	15.7	14.1	0	18.9
Hypersensitivity	56.3	20.3	23.6	7.0	13.9	17.5
Nausea	31.7	67.8	0	21.1	0	18.9
Arthralgia	7.0	13.6	7.9	7.0	20.9	11.6
Dizziness	3.5	40.7	0	7.0	7.0	11.6

Myalgia	10.6	13.6	3.9	7.0	7.0	7.3
Oedema peripheral	14.1	0	11.8	0	0	4.4
Hypertension	10.6	0	3.9	14.1	0	4.4
Injection-related reaction	14.1	33.9	0	0	0	7.3
Migraine	3.5	20.3	0	0	20.9	8.7
Vomiting	10.6	6.8	3.9	7.0	0	4.4

*As assessed by the investigator

†Preferred term was only reported from studies where an IV formulation was used

‡Numbers represent the frequency of events per 1,000 subject-years of exposure

Abbreviations: IV; intravenous, Pt; patient, SC; subcutaneous

B.3.10.1.2 Mepolizumab serious adverse events

A total of 155 subjects in three included studies (MEA112997 [DREAM], MEA115588 [MENSA], MEA115575 [SIRIUS]) reported serious adverse events; 15% in the placebo group, 6% in the mepolizumab 100 mg SC group and 10% in the mepolizumab 75 mg IV group (Table 49). The incidence of serious adverse events in the mepolizumab groups was similar to or less than the placebo group for all other serious adverse events. Comparable results were observed in the Phase 3b MUSCA study.

Table 49 On-treatment serious adverse events occurring in more than one patient (safety population)

Serious adverse event (preferred term)	**Number (%) patients**					
	Placebo N=412	***Mepolizumab***				
		100 SC N=263	*75 IV N=344*	*250 IV N=152*	*750 IV N=156*	*All doses N=915*
Any event	63 (15)	17 (6)	34 (10)	23 (15)	18 (12)	92 (10)
Asthma	38 (9)	5 (2)	20 (6)	15 (10)	9 (6)	49 (5)
Pneumonia	3 (<1)	1 (<1)	1 (<1)	0	2 (1)	4 (<1)
Nephrolithiasis	3 (<1)	1 (<1)	0	0	0	1 (<1)
Bronchitis	2 (<1)	0	1 (<1)	0	0	1 (<1)
Lobar pneumonia	1 (<1)	0	2 (<1)	0	0	2 (<1)
Tendon rupture	1 (<1)	0	1 (<1)	0	1 (<1)	2 (<1)
Atrial flutter	1 (<1)	1 (<1)	0	0	0	1 (<1)
Cerebrovascular accident	2 (<1)	0	0	0	0	0
Herpes zoster	0	2 (<1)	0	0	0	2 (<1)
Hypersensitivity	1 (<1)	1 (<1)	0	0	0	1 (<1)
Hypertension	0	0	1 (<1)	0	1 (<1)	2 (<1)
Myocardial ischaemia	0	0	1 (<1)	0	1 (<1)	2 (<1)
Viral upper respiratory tract infection	1 (<1)	0	1 (<1)	0	0	1 (<1)
Exposure adjusted*						
Serious adverse event (preferred term)	*Placebo Pt years = 284*	***Mepolizumab***				
		100 SC Pt years = 147	*75 IV Pt years = 254*	*250 IV Pt years = 142*	*750 IV Pt years = 144*	*All doses Pt years = 687*

Any event	348.6	189.9	204.5	232.1	188.1	203.7
Asthma	193.7	61.0	94.4	112.5	76.7	87.3
Pneumonia	10.6	6.8	3.9	0	13.9	5.8
Nephrolithiasis	10.6	6.8	0	0	0	1.5
Bronchitis	7.0	0	3.9	0	0	1.5
Lobar pneumonia	3.5	0	7.9	0	0	2.9
Tendon rupture	3.5	0	3.9	0	7.0	2.9
Atrial flutter	3.5	6.8	0	0	0	1.5
Cerebrovascular accident	7.0	0	0	0	0	0
Herpes zoster	0	13.6	0	0	0	2.9
Hypersensitivity	3.5	6.8	0	0	0	1.5
Hypertension	0	0	3.9	0	7.0	2.9
Myocardial ischaemia	0	0	3.9	0	7.0	2.9
Viral upper respiratory tract infection	3.5	0	3.9	0	0	1.5
*Numbers represent the frequency of events per 1,000 subject-years of exposure. Abbreviations: IV; intravenous, Pt; patient, SC; subcutaneous						

A total of five deaths were reported across the included studies; two patients (<1%) were receiving placebo ([1] road traffic accident and [2] aspiration secondary due to gastrointestinal haemorrhage) and three patients (<1%) were receiving mepolizumab ([1] severe acute pancreatitis and septic shock, [2] severe acute asthma exacerbation and [3] asphyxia due to suicide by hanging in one patient).

B.3.10.1.3 Mepolizumab adverse reactions from Summary of Product Characteristics

A total of 896 adults and 19 adolescent subjects with severe refractory eosinophilic asthma received either a SC or an IV dose of mepolizumab during three placebo-controlled clinical studies of 24–52 weeks' duration. The table below presents the adverse reactions from the two placebo-controlled studies in patients receiving mepolizumab 100 mg SC (n=263).

The safety profile of mepolizumab in severe refractory eosinophilic asthma patients (n=998) treated for a median of 2.8 years (range: 4 weeks to 4.5 years) in open-label extension studies was similar to that observed in the placebo-controlled studies.

The frequency of adverse reactions is defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 50 Frequency of adverse reactions by system organ class

System organ class	Adverse reactions	Frequency
Infections and infestations	Lower respiratory tract infection Urinary tract infection Pharyngitis	Common
Immune system disorders	Hypersensitivity reactions (systemic allergic)* Anaphylaxis†	Common Rare
Nervous system disorders	Headache	Very common
Respiratory, thoracic and mediastinal disorders	Nasal congestion	Common
Gastrointestinal disorders	Abdominal pain upper	Common
Skin and subcutaneous tissue disorders	Eczema	Common
Musculoskeletal and connective tissue disorders	Back pain	Common
General disorders and administration site conditions	Administration-related reactions (systemic non-allergic)‡ Local injection site reactions Pyrexia	Common
*Systemic reactions including hypersensitivity have been reported at an overall incidence comparable to that of placebo †From spontaneous post-marketing reporting ‡The most common manifestations associated with reports of systemic non-allergic administration-related reactions were rash, flushing and myalgia; these manifestations were reported infrequently and in <1% of subjects receiving mepolizumab 100 mg subcutaneously		

B.3.10.2 Reslizumab reported adverse event profile

Across the four randomised, placebo-controlled trials included in this submission, (Study 3081,[34] Study 3082,[35] Study 3083,[35] Study 3084[36]) reslizumab was generally

well tolerated. The adverse event profile reported for the studies is detailed in Table 51.

The most common adverse events recorded by patients receiving reslizumab during the studies were worsening of asthma, upper respiratory tract infection, nasopharyngitis, sinusitis and headache (Table 52). Injection site reactions were only reported in the jointly reported studies (Study 3082 and Study 3083), during which 1–2% of patients receiving reslizumab and <1–3% of patients receiving placebo had such complications.[35] Although in a low number of patients, two studies reported anaphylactic reactions: two patients from Study 3083 and two patients from Study 3084 (one event was considered related to ongoing allergen immunotherapy, not reslizumab).[35,36] Anti-drug antibody testing was completed in all studies. Across these studies, 2–12% of patients tested positive but this includes baseline assessments. Most patients only tested positively once over the treatment period and at low titre levels. The adverse event profile for those testing positive was generally similar to the general, study population.

Table 51 Comparative summary of the adverse event profile for reslizumab studies

Trial number (acronym)	Study 3081[34]			Study 3082[35]		Study 3083[35]		Study 3084[36]	
	Placebo	*Reslizumab*		*Placebo*	*Reslizumab 3.0 mg/kg*	*Placebo*	*Reslizumab 3.0 mg/kg*	*Placebo*	*Reslizumab 3.0 mg/kg*
		0.3 mg/kg	*3.0 mg/kg*						
All adverse events (%)	66 (63)	59 (57)	61 (59)	206 (85)	197 (80)	201 (87)	177 (76)	72 (74)	218 (55)
Mild	–	–	–	41 (17)	68 (28)	36 (16)	67 (29)	–	–
Moderate	–	–	–	133 (55)	107 (44)	104 (60)	98 (42)	–	–
Severe	4 (4)	2 (2)	7 (7)	32 (13)	22 (9)	25 (11)	12 (5)	10 (10)	25 (6)
Worsening of asthma	20 (19)	6 (6)	16 (16)	127 (52)	97 (40)	119 (51)	67 (29)	19 (20)	50 (13)
Drug-related	8 (8)	6 (6)	12 (12)	36 (15)	36 (15)	27 (12)	34 (15)	16 (16)	28 (7)
Mild	–	–	–	23 (19)	24 (10)	14 (6)	22 (9)	–	–
Moderate	–	–	–	13 (5)	9 (4)	13 (6)	11 (5)	–	–
Severe	1 (<1)	0	1 (<1)	0	3 (1)	0	1 (<1)	0	2 (1)
Leading to discontinuation/ withdrawal	10 (10)	1 (<1)	6 (6)	8 (3)	4 (2)	9 (4)	8 (3)	12 (12)	29 (7)
Serious adverse events (%)	<1	0	4	34 (14)	24 (10)	23 (10)	18 (8)	4	4
Drug-related	0	0	0	–	–	–	–	–	–
Fatal	0	0	0	1 (<1)	0	0	0	0	0

Table 52 Comparative summary of the adverse events occurring in ≥5 patients across the reslizumab studies

Trial number (acronym) / N (%)	Study 3081[34]			Study 3082[35]		Study 3083[35]		Study 3084†[36]	
	Placebo	*Reslizumab*		*Placebo*	*Reslizumab 3.0 mg/kg*	*Placebo*	*Reslizumab 3.0 mg/kg*	*Placebo*	*Reslizumab 3.0 mg/kg*
		0.3 mg/kg	*3.0 mg/kg*						
Asthma (exacerbation*)	20 (19)	6 (6)	16 (16)	127 (52)	97 (40)	118 (51)	67 (29)	19 (20)	50 (13)
Upper respiratory tract infection	3 (3)	3 (3)	5 (5)	32 (13)	39 (16)	16 (7)	8 (3)	11 (11)	42 (11)
Nasopharyngitis	4 (4)	6 (6)	6 (6)	33 (14)	28 (11)	56 (24)	45 (19)	5 (5)	13 (3)
Sinusitis				29 (12)	21 (9)	–	–	7 (7)	22 (6)
Headache	6 (6)	8 (8)	11 (11)	30 (12)	19 (8)	17 (7)	33 (14)	4 (4)	13 (3)
Influenza				23 (9)	18 (7)	–	–	3 (3)	8 (2)
Bronchitis	5 (5)	5 (5)	2 (2)	24 (10)	13 (5)	–	–	6 (6)	14 (4)
Back pain				13 (5)	13 (5)	8 (3)	12 (5)	3 (3)	6 (2)
Urinary tract infection				11 (5)	13 (5)	–	–	0	10 (3)
Oropharyngeal pain				8 (3)	13 (5)	–	–	3 (3)	4 (1)
Allergic rhinitis				6 (2)	13 (5)	–	–	3 (3)	9 (2)
Nausea				10 (4)	12 (5)	–	–	5 (5)	3 (<1)
Cough				13 (5)	11 (4)	–	–		
Pharyngitis				13 (5)	10 (4)	–	–		
Dyspnoea				12 (5)	10 (4)	–	–		
Fatigue				11 (5)	6 (2)	–	–		
Dizziness				13 (5)	5 (2)	–	–	3 (3)	3 (<1)
Acute sinusitis								3 (3)	6 (2)
Diarrhoea								3 (3)	4 (1)
Viral gastroenteritis								3 (3)	4 (1)
Arthralgia								4 (4)	3 (<1)
Contusion								3 (3)	3 (<1)
Dysgeusia								3 (3)	3 (<1)
Gastroenteritis								3 (3)	0
*Exacerbation specified for Study 3081 only; †Occurring in ≥3% of patients in either group									

B.3.10.3 Benralizumab summarised adverse event profile

As reported in the benralizumab submission (TA565), across the three trials (SIROCCO, CALIMA and ZONDA), the rates of adverse events and serious adverse events were numerically lower for benralizumab Q8W compared with placebo. Any adverse event was reported by 68–75% of patients receiving benralizumab versus 76–83% for patients receiving placebo. Rates of serious adverse events ranged from 9–13% for benralizumab and from 14–19% for placebo. The most commonly experienced adverse events across the trials included worsening asthma, nasopharyngitis, upper respiratory tract infection, headache and bronchitis. Hypersensitivity reactions were infrequent and similar between arms.

Table 53 Summary of adverse events for benralizumab studies: SIROCCO, CALIMA and ZONDA

N (%)	Placebo	Benralizumab 30 mg Q8W	Risk difference (%)	Relative risk (95% CI)
SIROCCO number of patients	407	394		
Any adverse event	311 (76)	281 (71)	–5.1	0.93 (0.86, 1.01)
Any adverse event leading to treatment discontinuation	3 (<1)	8 (2)*	1.3	2.75 (0.74, 10.31)
Any serious adverse event	55 (14)	52 (13)	–0.3	0.98 (0.69, 1.39)
Death	2 (1)	1 (<1)	–0.2	0.52 (0.05, 5.67)
CALIMA number of patients	440	428		
Any adverse event	342 (78)	320 (75)	–3.0	0.96 (0.89, 1.04)
Any drug-related adverse event	36 (8)	54 (13)	4.4	1.54 (1.03, 2.30)
Any adverse event leading to treatment discontinuation	4 (<1)	10 (2)	1.4	2.57 (0.81, 8.13)
Any adverse event leading to death	0	2 (<1)	0.5	5.14 (0.25, 106.75)
Any serious adverse event	60 (14)	40 (9)	–4.3	0.69 (0.47, 1.00)
ZONDA number of patients	75	73		
Any adverse event	62 (83)	55 (75)	–7.3	0.91 (0.77, 1.08)
Any adverse event leading to treatment discontinuation	2 (3)	3 (4)	1.4	1.54 (0.27, 8.96)
Any adverse event leading to death	0	2 (3)	2.7	5.13 (0.25, 105.17)
Any serious adverse event	14 (19)	7 (10)	–9.1	0.51 (0.22, 1.20)
Abbreviations: CI; confidence interval, Q8W; every 8 weeks				

B.3.10.4 Conclusions on the safety of the technology being appraised

This safety summary demonstrates that mepolizumab is well tolerated in severe refractory eosinophilic asthma patients receiving optimised standard of care. The safety profile is similar to patients receiving placebo added to optimised standard of care, with the exception of an increased rate of local site reactions with mepolizumab. While the certainty of the safety profile of any medicine is limited to the breadth of exposure in studies, the data do not suggest evidence of a differential treatment response across the studied patient populations.

B.3.11 Conclusions about comparable health benefits and safety

B.3.11.1 Efficacy and safety conclusions comparing mepolizumab versus reslizumab and benralizumab

Asthma exacerbations are a primary cause of morbidity and mortality in patients with asthma and drive healthcare use and costs.[50] The significant improvement in the rate of clinically significant exacerbations observed with all three treatments versus placebo in the ITT population seen here is in accordance with previous meta-analyses of anti-IL-5 pathway-directed therapies in patients with severe asthma.[40,51]

A safety analysis was carried out in the recent Cochrane review and found that there were no excess serious adverse events with any anti-IL-5 pathway-directed treatment, and that there was a reduction of serious adverse events in favour of mepolizumab versus placebo that might be attributable to a beneficial effect on asthma-related serious adverse events.[40]

B.3.11.2 Differences in effectiveness between mepolizumab, reslizumab and benralizumab

Based on the indirect treatment comparison, mepolizumab significantly reduced the rate of clinically significant exacerbations by 34–45% compared with benralizumab across all baseline blood eosinophil count thresholds and by 45% compared with reslizumab in the 400 cells/mL or greater subgroup. Furthermore, mepolizumab was associated with significant improvements in patient-reported asthma control, as assessed by ACQ score, compared with reslizumab and benralizumab in the 400 cells/mL or greater subgroup and benralizumab in the 150 cells/mL or greater and 300 cells/mL or greater subgroups. A significant improvement in lung function of 110 mL (as assessed by change from baseline in pre-bronchodilator FEV_1) was observed for benralizumab versus reslizumab in patients with baseline blood eosinophil counts of 400 cells/mL or greater. However, when treatment comparisons used the ITT populations and did not take into account differences in baseline blood eosinophil count or ACQ score, there were no significant differences among the three treatments.

Although mepolizumab has demonstrated greater efficacy than benralizumab and reslizumab at all blood eosinophil count thresholds assessed for clinically significant exacerbations and ACQ scores, there was no statistically significant difference for exacerbations requiring ED visits/hospitalisations. This lack of difference for exacerbations requiring ED visits/hospitalisations is possibly because these are

infrequent events, and as such there might have been insufficient data to determine statistically significant differences between treatments for this endpoint.

In summary, from the data available for all three IL-5 treatments, it is clear that an assumption of at least similar efficacy can be made, and it is likely, based on the published indirect treatment comparison,[4] that mepolizumab may in fact provide superior benefit in some endpoints, for example the reduction in clinically significant exacerbations and patient-reported asthma control.

B.3.11.3 Plausibility of similarities and differences between mepolizumab, reslizumab and benralizumab

The differences reported in the indirect treatment comparison for mepolizumab versus benralizumab and reslizumab were observed despite inherent between-study variation in the mode of action of the study drugs, study drug preparation, dosing regimens, mode of delivery and background standard of care (mepolizumab 100 mg every 4 weeks [Q4W] SC and reslizumab 3 mg/kg Q4W IV injections are anti-IL-5 antibodies, whereas benralizumab is an anti-IL-5 receptor antibody administered at 30 mg Q8W subcutaneously). Given the well-documented importance of baseline blood eosinophil counts in individualising treatment for patients with severe asthma,[52] these results are of considerable interest clinically.

B.3.11.4 Review of preferred clinical assumptions focusing on key drivers of cost effectiveness

There was a challenge in assessing the effect on the incremental cost-effectiveness ratio (ICER) that mepolizumab, reslizumab and benralizumab had with respect to the reduction in the use of OCS. There is limited data to demonstrate the health-related quality of life associated with the reduction in use of OCS. In addition, some adverse effects associated with its prolonged use are irreversible. The model in TA565 for benralizumab was able to incorporate some data on the benefit of a reduction in usage and was accepted by the committee. The committee for mepolizumab also acknowledged that there were adverse effects associated with the use of long-term systemic corticosteroids that were not captured in the modelling, and accounting for these would reduce the ICER. The same conclusion was reached for reslizumab.

An upward adjustment in the exacerbation rate of the standard-of-care arm was applied in the economic model for reslizumab. This was not accepted by the committee and unadjusted baseline exacerbations were applied, as this was deemed to be the best data available for decision making. There would have been a lower ICER if this adjustment had been accepted. There was no adjustment to the standard-of-care arm in the benralizumab trial. The utilities across all the separate appraisals had minimal effect on cost effectiveness. There was an adjustment in the mepolizumab trial for a difference in the baseline utility values. This was because the EuroQol-5 Dimension (EQ-5D) values for the mepolizumab and standard-of-care groups differed at the start of the trial, despite randomisation. The committee heard from the company that this imbalance underestimated the improvement in EQ-5D scores in patients receiving mepolizumab compared with standard of care. The committee concluded baseline adjustment was appropriate for decision making.

The stopping rule appeared to have a nominal effect on the ICERs for mepolizumab, reslizumab and benralizumab. This is because all the medicines must be reassessed

every year in clinical practice to continue treatment. This was consistent for all three medicines and their published NICE guidance.

Both the committee and the Evidence Review Group (ERG) for TA565 concluded that both mepolizumab and benralizumab have similar clinical effectiveness and are cost effective for the eligible populations using the indirect comparison provided by the company. The company's indirect treatment comparison compared mepolizumab and benralizumab only. TA565 was unable to present data comparing benralizumab to reslizumab and assumed that both treatments had the same efficacy for the analyses. In the ERG analysis, benralizumab was clearly cost effective when compared with reslizumab.

The equivalent efficacy assumption for benralizumab and reslizumab resulted in benralizumab achieving a wider recommendation than mepolizumab. This submission addresses the evidence gap of comparing mepolizumab with reslizumab, with the inclusion of benralizumab for completeness.

In summary, the indirect treatment comparison and overall assessment of Phase 3 studies for the available anti-IL-5 pathway-directed therapies in patients with severe eosinophilic asthma show that mepolizumab, reslizumab and benralizumab all significantly reduce clinically significant exacerbations and improve asthma control and lung function versus placebo, with a comparable safety profile.

B.3.11.5 Uncertainties in the evidence

The indirect treatment comparison is subject to limitations common to such analyses. The included studies were conducted in different cohorts of patients, different regions over different periods of time, and within different healthcare delivery systems. These factors could all have an effect on observed treatment effects. For example, the definition of standard of care will have differed between the included trials, which might have influenced the observed treatment effects. However, considerable overlap existed between the different study populations, particularly when inclusion criteria for blood eosinophil counts and ACQ scores were matched.

The variation in study duration, ranging from 15–56 weeks, might have affected treatment comparisons. Although the change from baseline in each treatment varied through time, the treatment differences (between treatment and placebo) remained consistent from approximately 16 weeks onwards in the individual studies, meaning that differences in change from baseline ACQ score and FEV_1 reported from 15 weeks and up to 56 weeks could be compared without further correction. The effect measures used in this analysis (e.g. risk ratio for exacerbations rather than dichotomous outcomes, such as percentage of patients with >1 exacerbation) were appropriate for combining results from studies of different durations. Furthermore, there was no evidence of heterogeneity when combining studies of different durations. Therefore, the bias potentially caused by variations in study duration is likely to be small.

Slight variation in the definition of clinically significant exacerbations also existed between studies. It was not possible to conduct a meta-regression analysis adjusting for within-study and between-study variation in blood eosinophil counts or other baseline covariates because of the small number of studies included and the inconsistency of data reporting between included studies (e.g. geometric mean blood eosinophil counts vs non-geometric means).

A further limitation of the study was that the patient populations from the reslizumab studies could not be closely matched with regard to their exacerbation history or ICS use. Closer matching of exacerbation history is of particular importance given the effect of exacerbation history on treatment efficacy. Nonetheless, for the endpoint of exacerbations requiring ED visits/hospitalisations, patient subgroups were matched according to the presence of two or more historic exacerbations and the use of GINA Step 4/5 therapy.

An additional limitation is the use of different versions of the ACQ in different clinical trials (ACQ-7 in the reslizumab trials, ACQ-6 in the benralizumab trials and ACQ-5 in the mepolizumab trials). However, validation studies have been published showing that all ACQ versions have similar psychometric properties and produce similar results.[47,48] For the assessment of lung function, comparisons were based on FEV_1 in litres because percent-predicted FEV_1 was not available for the majority of the benralizumab or reslizumab studies, meaning the analysis could not account for potential differences in baseline lung function.

B.3.12 Ongoing studies

There are no ongoing studies for mepolizumab, reslizumab or benralizumab that are relevant for this submission.

B.4 Cost-comparison analysis

B.4.1 Changes in service provision and management

Mepolizumab, reslizumab and benralizumab are used in secondary or tertiary care settings. They are prescribed in specialist clinics for the treatment of patients with severe eosinophilic asthma. The main resource use associated with mepolizumab and its comparators are drug acquisition cost and administration costs.

Mepolizumab is available in three different formulations for subcutaneous injection: 100 mg powder for solution for injection, 100 mg solution in pre-filled pen and the 100 mg solution in pre-filled syringe. Reslizumab is available in two doses for intravenous (IV) infusion: a 2.5 mL vial and a 10 mL vial. Benralizumab is now available as a 30 mg pre-filled syringe and pre-filled pen. Reslizumab and mepolizumab have the same dosing schedule and are given to a patient every 4 weeks[53,54]. Benralizumab has a slightly longer schedule that is initially every 4 weeks for the first three doses, then every 8 weeks thereafter[55]

National Institute for Health and Care Excellence (NICE) technology appraisal (TA) 431 appraised the 100 mg mepolizumab powder for injectable solution. Since the appraisal, two pre-filled formulations are now licensed and available for subcutaneous injection. The pre-filled formulations are reimbursed by National Health Service (NHS) England and are available for use within the NHS under the same agreement as the powder for injectable solution.

Reslizumab requires additional resource compared with mepolizumab as the medicine must be prepared and administered through an IV infusion for 30 minutes, requiring a healthcare professional to be involved.[2] Mepolizumab is administered by subcutaneous injection and requires minimal administration time.[3] The pre-filled formulations of mepolizumab can be self-administered by the patient, their carers or a healthcare professional. Administration costs with the pre-filled formulations would be lower, as there would be less time spent preparing and administering when compared with the powder for solution for injection. Where patients can self-administer their mepolizumab dose, administration costs would be negligible, as a specialist nurse would not be required. The calculations assume that the first three doses of treatment will be administered under the training and supervision of a specialist nurse. Thereafter, the patient will be able to administer their regular doses without the supervision of a healthcare professional. This assumption is also applied to the benralizumab formulations.

All severe asthma patients who are initiating treatment must be monitored post-administration. A monitoring time of 15 minutes will be applied to all three medicines, this figure is taken from NICE TA431[1]. It is assumed that the monitoring time would be applicable for the first three doses of treatment, thereafter there will be no monitoring required. This assumption is applied to all three medicines.

Table 54 shows the allocated time required for the preparation, administration and monitoring of each treatment. They are reflective of the times expected in a clinical setting for patients with severe asthma.

Table 54 Comparing treatment preparation, administration and monitoring times associated with the different treatments and formulations in a clinical setting

	Mepolizumab 100 mg powder for solution for injection	Mepolizumab 100 mg solution for injection in pre-filled syringe or pen*	Reslizumab 10 mg/mL concentrate for solution for infusion	Benralizumab 30 mg pre-filled syringe or pen*
Preparation time	10 minutes	5 minutes	10 minutes	5 minutes
Administration time			30 minutes	
Monitoring time	15 minutes†	15 minutes†	15 minutes†	15 minutes†
Total time	25 minutes	20 minutes	55 minutes	20 minutes
Source	NICE TA431	NICE TA565	NICE TA479	NICE TA565
*Where a patient self-administers their medicine (mepolizumab and benralizumab pre-filled formulations), the first three doses of treatment will be given under the training and supervision of a specialist nurse, thereafter the patient will administer their own dose †The monitoring time is applied to the first three doses of treatment, thereafter the patient would not require monitoring for subsequent doses Abbreviations: NICE; National Institute for Health and Care Excellence, TA; technology appraisal				

B.4.2 Cost-comparison analysis inputs and assumptions

B.4.2.1 Features of the cost-comparison analysis

The cost comparison analysis will be confined to drug acquisition costs and administration costs. The patient access scheme (PAS) price for mepolizumab formulations will be applied in the analysis. The costs of reslizumab and benralizumab are commercial in confidence, so for this submission the respective list prices will be used.

A 1-year time horizon was applied, as this is when treatment is reassessed for effectiveness. A discount rate will not be applied as the time horizon is limited to 12 months. The analysis assumes that there are no differences in adverse event costs and that safety profiles are comparable. The analysis will include a comparison of 100 mg powder for solution for injection and the two pre-filled formulations of mepolizumab. This would demonstrate the potential savings in administration costs.

B.4.2.2 Intervention and comparators' acquisition costs

The PAS price for the mepolizumab formulations would be [redacted]. The list price of reslizumab is £499.99 per 100 mg vial and £124.99 per 25 mg vial will be used. As stated in section B.2.2, the dose for a 78 kg patient would be 225 mg. This would be at a total cost of £1,124.97 per dose. The list price for benralizumab is £1,995 per 30 mg pre-filled syringe.

Table 55 Acquisition costs of mepolizumab, reslizumab and benralizumab

	Mepolizumab 100 mg powder for solution for injection	Mepolizumab 100 mg solution for injection in pre-filled syringe or pen	Reslizumab 10 mg/mL concentrate for solution for infusion	Benralizumab 30 mg pre-filled syringe or pen
Pharmaceutical formulation(s)	100 mg powder for solution for injection	100 mg in pre-filled syringe 100 mg in pre-filled pen	Vial of 2.5 mL (25 mg) Vial of 10 mL (100 mg)	30 mg in pre-filled syringe 30 mg in pre-filled syringe
(Anticipated) care setting	Secondary or tertiary	Patient's home, secondary or tertiary	Secondary or tertiary	Patient's home, secondary or tertiary
Acquisition cost (excluding VAT)	[redacted]	[redacted]	£1,124.97 (List price)	£1,995 (List price)
Method of administration	SC injection	SC injection	IV infusion	IV infusion
Doses	13	13	13	8
Dosing frequency	Every 4 weeks	Every 4 weeks	Every 4 weeks	Every 4 weeks for the first three doses, then every 8 weeks
Dose adjustments	N/A	N/A	N/A	N/A
Average length of a course of treatment	Long term	Long term	Long term	Long term
Average cost of a course of treatment (acquisition costs only)	List price: £840 × 13 administrations = £10,920 [redacted]	List price: £840 × 13 administrations = £10,920 [redacted]	£14,624.61 per annum	£15,960 per annum
(Anticipated) average interval between courses of treatment	N/A	N/A	N/A	N/A
(Anticipated) number of repeat courses of treatment	N/A	N/A	N/A	N/A
Abbreviations: IV; intravenous, PAS; patient access scheme, SC; subcutaneous				

B.4.2.3 Intervention and comparators' healthcare resource use and associated costs

Mepolizumab

The unit cost of administration for the mepolizumab 100 mg powder for solution for injection are taken from the committee papers from TA431.[1] The unit cost of a specialist asthma nurse was £100 per hour.[1] It was assumed that it would take 10 minutes to prepare and administer a dose of mepolizumab and a further 15 minutes of time to monitor the patient afterwards. Based on this, the administration cost per dose would be £41.67. It is assumed that monitoring time is not required after the first three doses and so the administration time is reduced from month 4 onwards.

For the pre-filled formulations, a specialist nurse could administer mepolizumab immediately as the pre-filled formulations do not require reconstitution. The preparation and administration time are assumed to be 5 minutes and a further 15 minutes of time to monitor the patient afterwards. Using the same unit cost applied in NICE TA431,[1] the total administration cost per dose would be £33.33 for the first three doses. The newer formulations of mepolizumab can be administered at home by the patient or their carer. This activity would not require a specialist asthma nurse to administer the dose, hence there would be no administration or monitoring costs attached to this activity. Treating patients on mepolizumab at home could release capacity in specialist asthma clinics. This would provide the potential to review severe asthma patients on the waiting list, or the resources could be allocated to other patients requiring specialist respiratory care.

Reslizumab

The administration time was assumed to be 55 minutes (10 minutes for treatment preparation, 30 minutes for treatment administration and 15 minutes to monitor the patient after treatment administration) from the appraisal consultation document in TA479.[2] Using the same unit cost applied in NICE TA431, the total administration cost per dose would be £91.67.

Benralizumab

The preparation and administration time applied to benralizumab was 5 minutes in TA565.[3]The same healthcare resource use and associated costs attributed to the mepolizumab pre-filled formulations will also be applied to benralizumab.

It is assumed for this analysis that patients are seen by hospital consultants for review of their asthma condition at the same frequency across all medicines, and so there are no differential costs to consider in the analysis.

Table 56 Resource costs of the intervention technologies

	Mepolizumab 100 mg powder for solution for injection	**Mepolizumab 100 mg solution for injection in pre-filled syringe or pen**	**Mepolizumab 100 mg solution for injection in pre-filled syringe or pen (self-administration)**
Administration costs	Specialist asthma nurse (£100 per hour)	Specialist asthma nurse (£100 per hour)	Specialist asthma nurse (£100 per hour)
Unit cost	£100 × (25/60) minutes = £41.67 for the first three doses, then £100 × (10/60) minutes = £16.67 for subsequent doses	£100 × (20/60) minutes = £33.33 for the first three doses, then £100 × (5/60) minutes = £8.33 for subsequent doses	£100 × (20/60) minutes = £33.33 for the first three doses, then No cost for subsequent doses as patient is self-administering
Cost (£), price year	£291.71	£183.29	£99.99
Source reference	NICE TA431	NICE TA431, NICE TA565	NICE TA431, NICE TA565
Rationale for source	Used in prior TA	Used in prior TAs	Used in prior TAs
Units per course of treatment			
Number of units	13	8	8
Source reference	NICE TA431	NICE TA431	NICE TA431
Rationale for source	Used in prior TA	Used in prior TA	Used in prior TA
Total cost of administration			
Per course of treatment	£41.67 for first three doses £16.67 thereafter	£33.33 for first three doses £8.33 thereafter	£33.33 for first three doses No costs thereafter
Over the full-time horizon	£291.71	£183.29	£99.99
Abbreviations: NICE; National Institute for Health and Care Excellence, TA; technology appraisal			

Table 57 Resource costs of the comparator technologies

	Reslizumab 10 mg/mL concentrate for solution for infusion	Benralizumab 30 mg pre-filled syringe or pen	Benralizumab 30 mg pre-filled syringe or pen (self-administration)
Administration costs	Specialist asthma nurse (£100 per hour)	Specialist asthma nurse (£100 per hour)	Specialist asthma nurse (£100 per hour)
Unit cost	£100 × (55/60) minutes = £91.67 – for the first three doses, then £100 × (10/60) minutes = £66.67 for subsequent doses	£100 × (20/60) minutes = £33.33 for the first three doses, then £100 × (5/60) minutes = £8.33 for subsequent doses	£100 × (20/60) minutes = £33.33 for the first three doses, then No cost for subsequent doses as patient is self-administering
Cost (£), price year	£941.71	£141.64	£99.99
Source reference	NICE TA431, NICE TA79	NICE TA431, NICE TA565	NICE TA431, NICE TA565
Rationale for source	Used in prior TA	Used in prior TAs	Used in prior TAs
Units per course of treatment			
Number of units	13	8	8
Source reference	NICE TA79	NICE TA565	NICE TA565
Rationale for source	Used in prior TA	Used in prior TA	Used in prior TA
Total cost of administration			
Per course of treatment	£91.67 for first three doses £66.67 thereafter	£33.33 for first three doses £8.33 thereafter	£33.33 for first three doses No costs thereafter
Over the full-time horizon	£941.71	£141.64	£99.99
Abbreviations: NICE; National Institute for Health and Care Excellence, TA; technology appraisal			

B.4.2.4 Adverse reaction unit costs and resource use

There are no adverse reaction unit costs or resource use that should be considered for this analysis.

B.4.2.5 Miscellaneous unit costs and resource use

There are no miscellaneous unit costs or resource use that should be considered for this analysis.

B.4.2.6 Clinical expert validation

Clinical expert validation of resource use and unit costs were not necessary for this cost comparison. The clinical pathway for patients with severe asthma has not changed since mepolizumab was approved. Figures and assumptions from TA431, TA479 and TA565 have previously been accepted by NICE, so the analysis assumes that clinical validation would not be necessary.

B.4.2.7 Uncertainties in the inputs and assumptions

All the assumptions for cost and resource use are consistent with the accepted figures and methods used in the previous respective TAs. For acquisition costs, the analysis compared mepolizumab's PAS price to the list price of reslizumab and mepolizumab. These list prices were used as reslizumab and benralizumab have confidential commercial agreements in place with NHS England.

B.4.3 Base-case results

The base case results are presented below. The figures consider the acquisition cost of the drugs and their respective administration times. No other costs were relevant to the technologies being compared. There is a detailed breakdown of costs and resource use within section B.4.2.

Table 58 Base-case results using list prices with a one-year time horizon

Technologies	Acquisition costs (£)	Administration costs (£)	Adverse event costs (£)	Other costs (£)	Total costs (£)
Mepolizumab 100 mg powder for solution for injection	10,920	291.71	NA	NA	11,211.71
Mepolizumab 100 mg solution for injection in pre-filled syringe or pen	10,920	183.29	NA	NA	11,103.29
Mepolizumab 100 mg solution for injection in pre-filled syringe or pen (self-administration)	10,920	99.99	NA	NA	11,019.99
Reslizumab 10 mg/mL concentrate for solution for infusion	14,624.61	941.71	NA	NA	15,566.32
Benralizumab 30 mg pre-filled syringe or pen	15,960.00	141.64	NA	NA	16,101.64
Benralizumab 30 mg pre-filled syringe or pen (self-administration)	15,960.00	99.99	NA	NA	16,059.99
Abbreviations: NA; not applicable					

Table 59 Base-case results using the mepolizumab PAS price with a one-year time horizon

Technologies	Acquisition costs (£)	Administration costs (£)	Adverse event costs (£)	Other costs (£)	Total costs (£)
Mepolizumab 100 mg powder for solution for injection	[redacted]	291.71	NA	NA	[redacted]
Mepolizumab 100 mg solution for injection in pre-filled syringe or pen	[redacted]	183.29	NA	NA	[redacted]
Mepolizumab 100 mg solution for injection in pre-filled syringe or pen (self-administration)	[redacted]	99.99	NA	NA	[redacted]
Reslizumab 10 mg/mL concentrate for solution for infusion	14,624.61	941.71	NA	NA	15,566.32
Benralizumab 30 mg pre-filled syringe or pen	15,960.00	141.64	NA	NA	16,101.64
Benralizumab 30 mg pre-filled syringe or pen (self-administration)	15,960.00	99.99	NA	NA	16,059.99
Abbreviations: NA; not applicable					

B.4.4 Sensitivity and scenario analyses

As discussed in section B.4.2, an uncertainty was the acquisition cost. The analysis compared mepolizumab's list and PAS prices to the list price of reslizumab and benralizumab. Assumptions and costs from TA431, TA479 and TA565 have been applied.

The administration costs of mepolizumab would vary depending on who administers the medicine and the formulations being used. The scenario with the lowest costs represents patients who are self-administering mepolizumab at home.

The table below demonstrates the uptake of mepolizumab's pre-filled formulations and the powder for solution for injection (Table 60). This change greatly increases the number of severe asthma patients who could self-administer their dose at home and reduce healthcare resource use and costs associated with administering the medicine.

A sensitivity/scenario analysis is provided to show the potential variation around administration costs (

Table 61, Table 62, Table 63). Internal data has been used to demonstrate the proportion of mepolizumab dose units supplied as pre-filled formulations.[56] The data will be used to model the number of patients that could potentially self-administer at home.

The latest figures show that [redacted] of mepolizumab units were supplied as pre-filled formulations.[56] A weighted cost between self-administration and patients receiving their dose from a specialist nurse will be applied. For the first analysis, the assumption will be that all 70% would be self-administering at home versus 30% receiving their dose from a specialist nurse. The analysis will also be carried out at levels of 50% and 25% self-administration, respectively. The same weighted cost will be applied to benralizumab in each analysis. The cost of administration of reslizumab will remain the same as patients would not be able to self-administer at home.

Table 60 Total proportion (%) of mepolizumab units supplied monthly

Proportion (%)	Mar 2019	Apr 2019	May 2019	June 2019	July 2019	Aug 2019	Sep 2019	Oct 2019	Nov 2019	Dec 2019	Jan 2020	Feb 2020
Mepolizumab 100 mg powder for solution for injection[1]	[redacted]											
Mepolizumab 100 mg solution for injection in pre-filled pen[1]	[redacted]											
Mepolizumab 100 mg solution for injection in pre-filled syringe[1]	[redacted]											
Total units[1]	[redacted]											
[redacted]												

Table 61 Sensitivity analysis of administration costs with 70% of severe asthma patients self-administering

Technologies	Administration costs (£)	Weighting (%)	TOTAL Administration Costs (£)	Total Cost (drug + admin) (£)
Mepolizumab 100 mg powder for solution for injection	291.71	30	157.51	[redacted]
Mepolizumab 100 mg solution for injection in pre-filled syringe or pen (Self-administration)	99.99	70		
Reslizumab 10 mg/mL concentrate for solution for infusion	941.71	100	941.71	15,566.32
Benralizumab 30 mg pre-filled syringe or pen	141.64	30	112.49	16,072.49
Benralizumab 30 mg pre-filled syringe or pen (Self-administration)	99.99	70		

Table 62 Sensitivity analysis of administration costs with 50% of severe asthma patients self-administering

Technologies	Administration costs (£)	Weighting (%)	Total administration costs (£)	Total Cost (drug + admin) (£)
Mepolizumab 100 mg powder for solution for injection	291.71	50	195.85	[redacted]
Mepolizumab 100 mg solution for injection in pre-filled syringe or pen (self-administration)	99.99	50		
Reslizumab 10 mg/mL concentrate for solution for infusion	941.71	100	941.71	15,566.32
Benralizumab 30 mg pre-filled syringe or pen	141.64	50	120.82	16,080.82
Benralizumab 30 mg pre-filled syringe or pen (self-administration)	99.99	50		

Table 63 Sensitivity analysis of administration costs with 25% of severe asthma patients self-administering

Technologies	Administration costs (£)	Weighting (%)	Total administration costs (£)	Total Cost (drug + admin)
Mepolizumab 100 mg powder for solution for injection	291.71	75	243.78	[redacted]
Mepolizumab 100 mg solution for injection in pre-filled syringe or pen (self-administration)	99.99	25		
Reslizumab 10 mg/mL concentrate for solution for infusion	941.71	100	941.71	15,566.32
Benralizumab 30 mg pre-filled syringe or pen	141.64	75	131.23	16,091.23
Benralizumab 30 mg pre-filled syringe or pen (self-administration)	99.99	25		

B.4.5 Subgroup analysis

No clinically relevant subgroups were identified or required for the cost-comparison analysis.

B.4.6 Interpretation and conclusions of economic evidence

The cost-comparison analysis has established that mepolizumab has a lower administration cost when compared with reslizumab. Mepolizumab has a similar cost profile to benralizumab when comparing the administration costs of the respective pre-filled formulations.

This analysis has been conducted using previously submitted evidence from the TAs of the respective medicines and additional information from the mepolizumab summary of product characteristics, which includes the new pre-filled syringe and pen. The figures include relevant assumptions, costs and resource use estimates that were accepted by the committee to reach their original recommendations. The cost-comparison analyses are generalisable to patients receiving biologics for the treatment of severe eosinophilic asthma in England and Wales. Using the base-case results, there are lower administration costs associated with mepolizumab, when comparing the 100 mg powder for solution for subcutaneous injection with the IV infusion required for reslizumab. The resulting difference is a potential saving of £650 per annum per patient.

The analysis also considers the newer formulations of mepolizumab (pre-filled syringe or pen) that were not available when the initial TA was completed by NICE. The pre-filled formulation's administration costs are lower by £750 per annum per patient, when compared to reslizumab. The administration costs could be negligible for the pre-filled formulations if administered by the patient or their carer at home. The total cost of administration is £99.99, as the first three doses require the training and supervision of a specialist nurse.

When compared with benralizumab, the pre-filled formulations of mepolizumab have a slightly higher administration cost by £41.65 per annum per patient. There is no difference in the cost per administration of each dose (£33.33). The additional cost is attributed to the more frequent dosing schedule of mepolizumab, resulting in a higher total cost per annum.

However, as shown in the base-case results, if patients are administering their medicines (benralizumab or mepolizumab) at home, the cost difference would be negligible (both £99.99) as a nurse would no longer be required to administer the pre-filled dose, after the first three doses. The sensitivity and scenario analyses in section B.4.4 also demonstrate the impact of different levels of uptake of the pre-filled formulations of mepolizumab. Increasing the number of severe asthma patients self-administering mepolizumab reduces the total cost associated with administration.

There is a limitation in the methodology as the analyses compare mepolizumab's discounted PAS price with the list prices of reslizumab and benralizumab due to the confidential commercial agreements in place with NHS England for both these medicines. The administration costs have been compared as this was the most robust comparison available between the technologies. Table 56 providing a cost comparison of list prices was included in the analysis for completeness.

TA565 was unable to robustly address the evidence gap of comparing mepolizumab and benralizumab with reslizumab using a matching-adjusted indirect comparison (MAIC). The ITC comparison provided in this submission provides strong, published evidence on the comparative efficacy of these three medicines.

The indirect treatment comparison[4] demonstrated that the clinical efficacy of mepolizumab is at least similar, when compared with reslizumab and benralizumab, respectively. Mepolizumab has been shown to have a lower administration cost than reslizumab and a similar administration cost to benralizumab. Based on the information provided in the NICE guidance TA565 when considering the confidential PAS prices for benralizumab and reslizumab, it is expected that the total annual costs for benralizumab and mepolizumab will be similar and indeed, mepolizumab is likely to be cheaper than reslizumab. Our analyses in this submission demonstrate that mepolizumab provides similar or greater health benefits at a similar or lower cost compared with the comparators for patients with severe refractory eosinophilic asthma.

Therefore, GSK believe that mepolizumab should be recommended for the same patient population as specified by NICE for benralizumab (TA565).

B.5 References

1. NICE. Mepolizumab for treating severe refractory eosinophilic asthma. Technology appraisal guidance [TA431]. (2017) Available at: https://www.nice.org.uk/guidance/ta431 (Accessed: 22 April 2020).
2. NICE. Reslizumab for treating severe eosinophilic asthma. Technology appraisal guidance [TA479]. (2017) Available at: https://www.nice.org.uk/guidance/ta479 (Accessed: 22 April 2020).
3. NICE. Benralizumab for treating severe eosinophilic asthma. Technology appraisal guidance [TA565]. (2019) Available at: https://www.nice.org.uk/guidance/ta565 (Accessed: 22 April 2020).
4. Busse W, Chupp G, Nagase H, Albers FC, Doyle S, Shen Q, et al. Anti-IL-5 treatments in patients with severe asthma by blood eosinophil thresholds: Indirect treatment comparison, J Allergy Clin Immunol. 2019;, 143(1):190-200.e20.
5. Nucala summary of product characteristics for mepolizumab. (2020) Available at: https://www.medicines.org.uk/emc/product/10563/smpc (Accessed: 22 April 2020).
6. Paediatric authorisation: 30.08.2018 https://www.gsk.com/en-gb/media/press-releases/european-commission-approves-nucala-mepolizumab-for-the-treatment-of-children-with-severe-asthma/
7. Authorisation for self-administration with pre-filled pen or pre-filled syringe 01.08.2019. https://www.gsk.com/en-gb/media/press-releases/nucala-receives-eu-approval-for-self-administration-by-patients-with-severe-eosinophilic-asthma/
8. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma, N Engl J Med. 2014;371(13):1198–207.
9. MIMS. Available at: https://www.mims.co.uk/drugs/respiratory-system/asthma-copd (Accessed: 22 April 2020).
10. British Thoracic Society and Scottish Intercollegiate Guideline Network. British guideline on the management of asthma. (2019) Available at: https://www.brit-thoracic.org.uk/quality-improvement/guidelines/asthma/ (Accessed: 22 April 2020).
11. Asthma UK. What is severe asthma? (2019) Available at: https://www.asthma.org.uk/advice/severe-asthma/what-is-severe-asthma/ (Accessed: 22 April 2020).
12. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma, Eur Respir J. 2014;43(2):343–73.
13. Asthma UK. Living in Limbo: the scale of unmet need in difficult and severe asthma. (2019) Available at: https://www.asthma.org.uk/69841483/globalassets/get-involved/external-

affairs-campaigns/publications/living-in-limbo/living-in-limbo---the-scale-of-unmet-need-in-difficult-and-severe-asthma.pdf (Accessed: 22 April 2020).

14. Hessel PA, Mitchell I, Tough S, Green FH, Cockcroft D, Kepron W, et al. Risk factors for death from asthma. Prairie Provinces Asthma Study Group, Ann. Allergy Asthma Immunol. 1999;83(5):362–68.
15. Rea HH, Scragg R, Jackson R, Beaglehole R, Fenwick J, and Sutherland DC. A case-control study of deaths from asthma, Thorax. 1986;41(11):833–39.
16. Wenzel SE. Severe asthma in adults, Exp Lung Res. 2005;31(Suppl. 1):22.
17. The ENFUMOSA Study Group. The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. European Network for Understanding Mechanisms of Severe Asthma, Eur Respir J. 2003;22(3):470–77.
18. Walford HH and Doherty TA. Diagnosis and management of eosinophilic asthma: a US perspective, J Asthma Allergy. 2014;7:53–65.
19. Wener RR and Bel EH. Severe refractory asthma: an update, Eur Respir Rev. 2013;22(129):227–35.
20. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial, Lancet. 2012;380(9842):651–59.
21. Katz LE, Gleich GJ, Hartley BF, Yancey SW, and Ortega HG. Blood eosinophil count is a useful biomarker to identify patients with severe eosinophilic asthma, Ann Am Thorac Soc. 2014;11(4):531–36.
22. Suruki RY, Gunsoy N, Shin JY, Daugherty J, Nelsen L, Bradford E, et al. The Identification and Description of Severe Asthma Patients in a Cross-Sectional Study — the Ideal Study, J Allergy Clin Immunol. 2016;137(2): AB103.
23. Shiner RJ, Nunn AJ, Chung KF, and Geddes DM. Randomised, double-blind, placebo-controlled trial of methotrexate in steroid-dependent asthma, Lancet. 1990;336(8708):137–40.
24. Davies H, Olson L, and Gibson P. Methotrexate as a steroid sparing agent for asthma in adults, Cochrane Database Syst Rev. 2000;2:CD000391.
25. Lock SH, Kay AB, and Barnes NC. Double-blind, placebo-controlled study of cyclosporin A as a corticosteroid-sparing agent in corticosteroid-dependent asthma, Am J Respir Crit Care Med. 1996;153(2):509–14.
26. Nizankowska E, Soja J, Pinis G, Bochenek G, Sładek K, Domagała B, et al. Treatment of steroid-dependent bronchial asthma with cyclosporin, Eur Respir J. 1995;8(7):1091–99.
27. Evans DJ, Cullinan P, and Geddes DM. Gold as an oral corticosteroid sparing agent in stable asthma, Cochrane Database Syst Rev. 2001;2:CD002985.
28. NHS England. Commissioning Medicines for Children in Specialised Services 170001/P https://www.england.nhs.uk/wp-content/uploads/2017/03/commissioning-medicines-children-specialised-services.pdf

29. NICE. Resource impact report: Reslizumab for treating severe eosinophilic asthma (TA479). (2017) Available at: https://www.nice.org.uk/guidance/ta479/resources/resource-impact-report-pdf-4607198317 (Accessed: 22 April 2020).
30. Cinqaero summary of product characteristics for reslizumab. (2018) Available at: https://www.medicines.org.uk/emc/product/4370 (Accessed: 14 October 2019).
31. NICE. Final appraisal document: Benralizumab for treating severe eosinophilic asthma. (2018) Available at: https://www.nice.org.uk/guidance/ta565/documents/final-appraisal-determination-document (Accessed: 22 April 2020).
32. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma, N Engl J Med. 2014;371(13):1189–97.
33. Chupp GL, Bradford ES, Albers FC, Bratton DJ, Wang-Jairaj J, Nelsen LM, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial, Lancet Respir Med. 2017;5(5):390–400.
34. Bjermer L, Lemiere C, Maspero J, Weiss S, Zangrilli J, and Germinaro M. Reslizumab for Inadequately Controlled Asthma With Elevated Blood Eosinophil Levels: A Randomized Phase 3 Study, Chest. 2016;150(4):789-98.
35. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials, Lancet Respir Med. 2015;3(5):355–66.
36. Corren J, Weinstein S, Janka L, Zangrilli J, Garin M. Phase 3 study of reslizumab in patients with poorly controlled asthma: effects across a broad range of eosinophil counts, Chest. 2016;150(4):799–810.
37. Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial, Lancet. 2016;388(10056):2115–27.
38. FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial, Lancet. 2016;388(10056):2128–41.
39. Centre for Reviews and Dissemination, University of York. Systematic Reviews: CRD's guidance for undertaking reviews in health care. (2009) Available at: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf (Accessed: 22 April 2020).

40. Farne HA, Wilson A, Powell C, Bax L, and Milan SJ. Anti-IL5 therapies for asthma, Cochrane Database Syst Rev. 2017;9:CD010834.
41. FitzGerald JM, Bleecker ER, Menzies-Gow A, Zangrilli JG, Hirsch I, Metcalfe P, et al. Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies, Lancet Respir Med. 2018;6(1):51-64.
42. Brusselle G, Germinaro M, Weiss S, and Zangrilli J. Reslizumab in patients with inadequately controlled late-onset asthma and elevated blood eosinophils, Pulm Pharmacol Ther. 2017;43:39–45.
43. Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study, Am J Respir Crit Care Med. 2011;184(10):1125–32.
44. Bucher HC, Guyatt GH, Griffith LE, and Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials, J Clin Epidemiol. 1997;50(6):683–91.
45. DerSimonian R and Laird N. Meta-analysis in clinical trials, Control Clin Trials. 1986;7(3):177–88.
46. Ortega HG, Yancey SW, Mayer B, Gunsoy NB, Keene ON, Bleecker ER, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies, Lancet Respir Med. 2016;4(7):549–56.
47. Juniper EF, Svensson K, Mörk AC, and Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire, Respir Med. 2005;99(5):553–8.
48. Wyrwich KW, Khan SA, Navaratnam P, Nolte H, and Gates DF Jr. Validation and agreement across four versions of the asthma control questionnaire in patients with persistent asthma, Respir Med. 2011;105(5):698–712.
49. Henriksen DP, Bodtger U, Sidenius K, Maltbaek N, Pedersen L, Madsen H, et al. Efficacy, adverse events, and inter-drug comparison of mepolizumab and reslizumab anti-IL-5 treatments of severe asthma - a systematic review and meta-analysis, Eur Clin Respir J. 2018;5(1):1536097.
50. Zeiger RS, Schatz M, Dalal AA, Qian L, Chen W, Ngor EW, et al. Utilization and Costs of Severe Uncontrolled Asthma in a Managed-Care Setting, J Allergy Clin Immunol Pract. 2016;4(1):120–29.e3.
51. Cabon Y, Molinari N, Marin G, Vachier I, Gamez AS, Chanez P, et al. Comparison of anti-interleukin-5 therapies in patients with severe asthma: global and indirect meta-analyses of randomized placebo-controlled trials, Clin Exp Allergy. 2017;47(1):129–38.
52. Yancey SW, Keene ON, Albers FC, Ortega H, Bates S, Bleecker ER, et al. Biomarkers for severe eosinophilic asthma, J Allergy Clin Immunol. 2017;140(6):1509–18.
53. NICE, 2016, Appraisal consultation document for reslizumab (TA479), https://www.nice.org.uk/guidance/ta479/documents/appraisal-consultation-document, Accessed 17 October 2019

54. NICE, 2016, Mepolizumab Committee Papers (TA431), https://www.nice.org.uk/guidance/ta431/documents/committee-papers
55. NICE, 2018, Chair's presentation: benralizumab for treating inadequately controlled asthma, https://www.nice.org.uk/guidance/ta565/documents/1-4, Accessed 22 April 2020
56. GSK, Internal Data on File, Accessed: 22 April 2020.
57. Khatri S, Moore W, Gibson PG, Leigh R, Bourdin A, Maspero J, et al. Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma, J Allergy Clin Immunol. 2019;143(5):1742–51.e7.
58. Khurana S, Brusselle GG, Bel EH, FitzGerald JM, Masoli M, Korn S, et al. Long-term Safety and Clinical Benefit of Mepolizumab in Patients With the Most Severe Eosinophilic Asthma: The COSMEX Study, Clin Ther. 2019;41(10):2041–56.e5.
59. Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium, J Allergy Clin Immunol. 2006;117(2):391e397.
60. Winthrop KL, Novosad SA, Baddley JW, Calabrese L, Chiller T, Polgreen P, et al. Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance, Ann Rheum Dis. 2015;74(12):2107e211.
61. Leung E, Al Efraij K, and FitzGerald JM. The safety of mepolizumab for the treatment of asthma, Expert Opin Drug Saf. 2017;16(3):397–404.

B.6 Appendices

The following appendices relating to this submission are provided in a separate Appendix document:

- Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)
- Appendix D: Checklist of confidential information
- Appendix E: Identification, selection and synthesis of clinical evidence
- Appendix F: Adverse reactions

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisal

Mepolizumab for treating severe eosinophilic asthma [ID3750]

Clarification questions

June 2020

File name	Version	Contains confidential information	Date
ID3750_Mepolizumab asthma ERGClarification to company [ACIC]	01	Yes	30-Jun-2020

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Literature searches

A1. Please could the company clarify whether PubMed was the only source searched for the literature search on 14 January 2020, or whether any additional sources were searched? [Appendix E, Section E.1.1, p25.] If other sources were searched, please provide details of which sources, and the search strategies used.

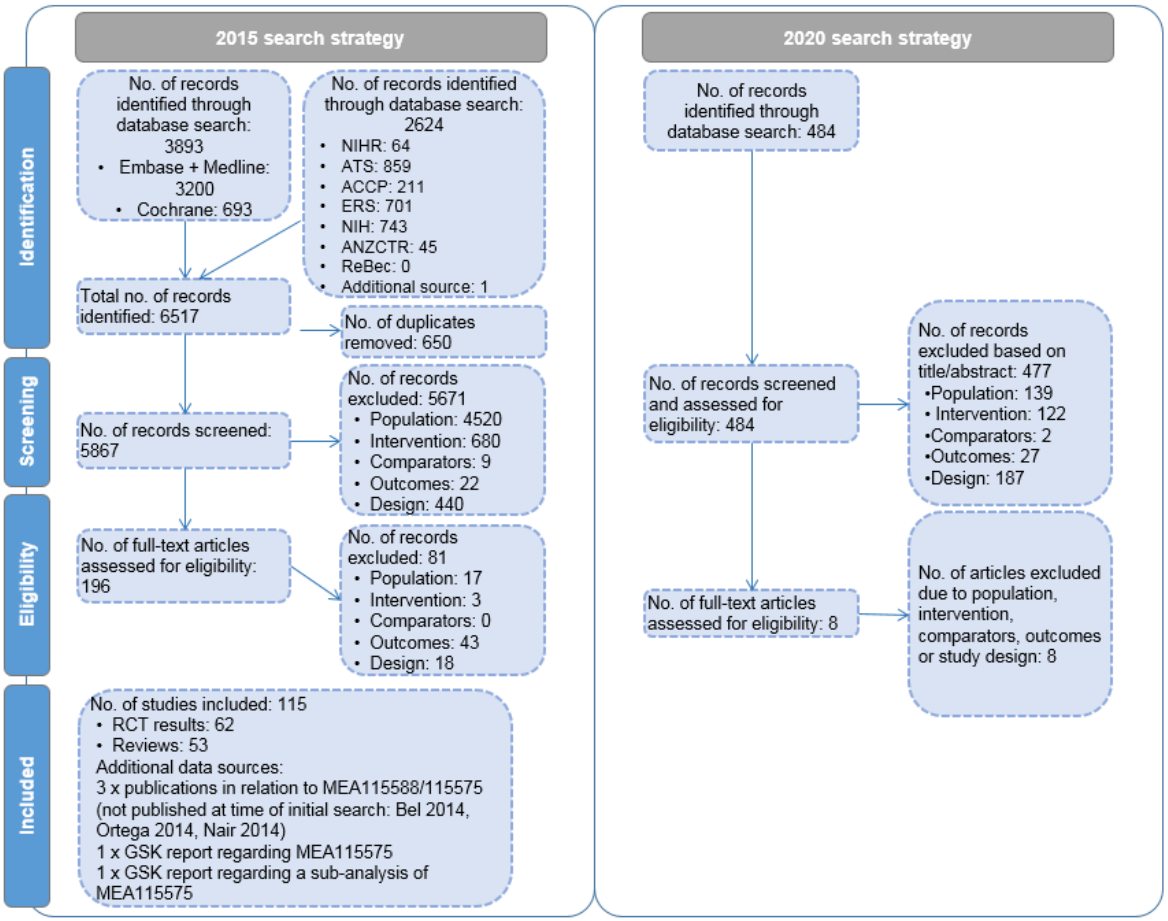
PubMed was the only source searched for the updated literature search on 14 January 2020. The literature search conducted as part of the mepolizumab single technology appraisal (STA) conducted on the 16 July 2015 used Medline, Medline In-Process and Embase as search sources. The purpose of January 2020 search was to identify other relevant evidence that may have been published since the original STA or to identify other relevant evidence published since the Busse et al. 2018 indirect treatment comparison (ITC).

For the Busse et al. ITC, the primary source was the published Cochrane review of anti–IL-5 pathway–directed therapies developed in severe asthma. The search strategy used for conducting the systematic review, which was undertaken to identify randomised placebo-controlled trials comparing mepolizumab, reslizumab, or benralizumab in adults and adolescents with asthma, is detailed within the Cochrane report (Cochrane searches carried out in March 2017). As stated in the ITC publication, additional searches were carried out in January 2018. Any publications from ongoing studies identified by the Cochrane report that might have been

published since March 2017 were also searched. The European Medicines Agency, US Food and Drug Administration, NICE documents and ClinicalTrials.gov postings were checked to identify any additional published subgroup analyses. In addition, any published meta-analyses for reslizumab and benralizumab using individual patient data potentially investigating subgroups were identified by searching PubMed.

A2. Regarding the PRISMA flow diagram [Appendix E, Fig 46, p43], please could the company confirm whether both sides of this table refer to the 2020 searches (as described in the headings); or whether the diagram on the left in fact refers to the 2015 searches, while the diagram on the right refers to the 2020 searches?

The diagram on the left in Figure 43 in our submission was incorrectly labelled. The left diagram refers to the 2015 searches from the original STA and the right diagram refers to the 2020 searches. The updated diagram is presented below:



Clinical effectiveness evidence

A3. While the ERG acknowledges that this appraisal is an FTA, the submission lacks clarity and consistency in reporting, particularly in respect of the study selection process. Please comment in respect of the following:

a) **There is inconsistency in study selection criteria between Table 66 (Appendix E) and Section B.3.1; e.g. outcomes (ICS/OCS use included in Table 66 but not specified in Section B.3.1). Please clarify which selection criteria were used to identify studies that were eligible for inclusion in the submission, including whether the criteria were different for the identification of clinical evidence (Section B.3.2) vs the inclusion criteria for the indirect treatment comparison (ITC).**

The submission includes the Busse et al. indirect treatment comparison (ITC) as the key comparative efficacy data for mepolizumab versus benralizumab and reslizumab. In Section B.3.1 and for completeness, we have provided an overview of the phase 2b and phase 3 studies for reslizumab, benralizumab and mepolizumab from the respective clinical development programmes. Appendix E details the searches conducted as part of the original STA in 2015 as well as an updated search conducted in January 2020. Appendix E does not refer to the study selection criteria/PICOS for the ITC, this is provided below. An updated search of the literature conducted in January 2020 has confirmed that no direct comparative evidence or other relevant placebo controlled RCTs have been published since the Busse et al. ITC was published in 2018. Therefore, the ITC remains a current and robust comparative analysis of evidence for the anti-IL5 class.

The key efficacy data for this submission is the published Busse et al. ITC. This was a peer-reviewed analysis providing efficacy comparisons across three key outcomes for the three anti-IL-5s stratified by baseline blood eosinophil counts. The studies included in the ITC are considered the most relevant to this decision problem as they comprise data for the licensed doses and reflected availability within UK clinical practice. Studies eligible for inclusion in this ITC were required to meet a predefined Population, Intervention, Comparator, Outcomes, Study Design (PICOS) framework. The populations consisted of patients with SEA aged 12 years or greater. Only those assessing approved doses or formulations of licensed anti–IL-5 pathway–directed treatments were included (100 mg of mepolizumab administered subcutaneously every 4 weeks [Q4W], 3 mg/kg reslizumab Q4W, and 30 mg of benralizumab every 8 weeks [Q8W; three 4-weekly doses followed by 8-weekly dosing]) to ensure interventions reflected

availability within clinical practice. The comparators in the phase 3 studies included placebo only, based on the regulatory clinical development programmes; there were no trials directly comparing the anti-IL-5s. The outcomes included in the ITC analysis were clinically significant exacerbations, defined as an exacerbation requiring treatment with OCSs/systemic corticosteroids (for patients on maintenance OCSs, a >2-fold increase in dose was required) or requiring an emergency department (ED) visit or hospitalization; exacerbations requiring an ED visit/hospitalization; ACQ score (any version); and change from baseline pre-bronchodilator FEV_1. Finally, all included studies had a randomised, double-blind, controlled study design. There were no restrictions on study timeframe or duration.

b) In Section B.3.2.3 it is stated that "Two relevant, randomised, controlled, clinical trials have been included in this submission for benralizumab: SIROCCO and CALIMA." However, in the presentation of efficacy and safety results, reference is made to three trials SIROCCO, CALIMA, and ZONDA. Please clarify whether ZONDA is in scope of this appraisal – it appears relevant vs specified criteria in Table 66.

The ZONDA trial was designed to demonstrate the efficacy and safety of benralizumab in reducing oral corticosteroid (OCS) dose in severe asthma patients dependent on maintenance OCS. The SIRIUS trial was also designed to demonstrate the efficacy and safety of mepolizumab in reducing OCS dose in severe asthma patients dependent on maintenance OCS. The study designs and endpoints prevent inclusion of the OCS-reduction studies as part of the ITC. A summary of efficacy and safety results from ZONDA and SIRIUS were included in the submission for completeness and in support of the comparable efficacy demonstrated for benralizumab and mepolizumab in the ITC.

c) There appear to be discrepancies in the reported study selection process, e.g. the PRISMA flow chart (Figure 46, Appendix E) indicates 62 RCTs were included in the prior submission. Were these studies rescreened versus eligibility criteria for this appraisal? Was the list of 28 excluded studies in Table 68 (Appendix E) a result of rescreening the 62 RCTs from TA431?

The list of 28 excluded studies in Table 68 (Appendix E) is a copy of Table 21 from Appendix 8.2.3 from the original mepolizumab STA (TA431) and lists the studies that were deemed not relevant and therefore, excluded from the original

STA. Studies excluded in the previous submission were not rescreened for this appraisal.

An updated search was conducted to identify whether there were additional relevant studies published since the original TA431 searches. For the search conducted in January 2020, eligibility of articles was assessed by an independent researcher, based on the pre-specified PICOS and inclusion and exclusion criteria (see Table 66). Selection was firstly based on title and abstract, but where inclusion still remained unclear, full texts were evaluated. The comparators considered for this appraisal were placebo, reslizumab and benralizumab.

d) Table 67 lists eight studies whereas the excluded studies reported in the PRISMA flow chart indicates seven studies were excluded.

The PRISMA flow diagram (Fig 46) should state that 8 studies were excluded. Please see updated diagram in Question A2 above.

A4. Please clarify the following for: (i) patients with a blood eosinophil count of ≥300 cells per microlitre; (ii) patients with a blood eosinophil count of ≥300 cells per microlitre who have had ≥3 severe asthma exacerbations in the previous 12 months; and, (iii) patients with a blood eosinophil count of ≥300 cells per microlitre who have had ≥4 severe asthma exacerbations in the previous 12 months groups or provide rationale for omissions where information is not available.

a) Study selection criteria and process for studies reporting data for the specified subgroup (list of included studies and rationale for any exclusions per the specified criteria)

b) Baseline demographics and clinical characteristics for the specified subgroup in each included trial.

Mepolizumab

Please see tables for mepolizumab provided for question A11 below. Demographic and baseline characteristic data have been provided for MUSCA, MENSA and DREAM studies, grouped by dose of mepolizumab for the subgroup of patients with a blood eosinophil count of ≥300 cells per microlitre who have had ≥4 severe asthma exacerbations in the previous 12 months.

Benralizumab:

Having reviewed the NICE committee documents for the benralizumab appraisal (TA565) we were unable to locate unredacted data (demographic and baseline characteristics, efficacy or safety) in the subgroup comprising patients with a blood eosinophil count of ≥300 cells per microlitre who have had ≥4 severe asthma exacerbations in the previous 12 months. However we did find the detailed tables below which provide baseline data for the ITT population to support the manufacturer's submitted analyses for the two benralizumab Phase 3 studies: SIROCCO and CALIMA, for the two Phase 3 studies MENSA and DREAM (which were included in their base case MAIC analysis) and for the two pivotal Phase 3 studies (3082 and 3083) and the pooled analysis of these two studies for reslizumab. In Question A11 we have also included the table that was provided in the ITC additional results section which shows an indirect comparison of mepolizumab and benralizumab for this subgroup.

Table A4.1: Summary of demographic and baseline characteristics for key Phase 3 studies for benralizumab, mepolizumab and reslizumab – ITT Population

Characteristics	SIROCCO		CALIMA		MENSA			DREAM	
Population	Overall		HD ICS subgroup		Overall			Overall	
	BENRAQ8W N=398	Placebo N=407	BENRA Q8W N=364	Placebo N=370	MEPO 100 mg SC N=194	MEPO 75 mg IV N=191	Placebo N=191	MEPO 75 mg IV N=153	Placebo N=155
Age, years	47.6 (14.5)	48.7 (14.9)	50.1 (13.3)	49.8 (14.3)	51.2 (14.55)	50.0 (14.03)	49.2 (14.26)	50.2 (11.3)	46.4 (10.8)
Gender, % male	36.7	33.9	38.2	40.3	40.0	45.0	44.0	32.0	37.0
White, % patients	72.1	74.2	85.2	86.8	77.0	79.0	77.0	91.0	90.0
Black, % patients	3.8	3.9	3.6	3.2	4.0	3.0	2.0	3.0	4.0
Asian, % patients	12.6	12.3	11.0	10.0	18.0	17.0	20.0	5.0	6.0
Other, % patients	11.6	9.6	0.3	0.0	1.0	1.0	1.0	1.0	0.0
Body mass index	28.21 (6.18)	28.93 (7.07)	29.0 (6.5)	29.25 (6.54)	27.60 (5.58)	27.68 (5.68)	28.04 (5.58)	28.4 (6.0)	28.3 (6.1)
FEV1 predicted (%)	56.1$	56.6$	56.9	57.5	59.3	61.4	62.4	60$	59$
Morning PEF (L/min)	233.12	230.83	241.85	242.16	255.3	268.6	277	-	-
FEV1/FVC (%)	65	66	64	65	66	67	67	68	67
FEV1 pre-bronch. (L)	1.68	1.66	1.72	1.76	1.73	1.85	1.86	1.81$	1.90$
Reversibility (%)	27.2	25.5	25.1	27.2	27.9$	25.4$	27.4$	22.6^	26.8^
ACQ scores**	2.8	2.87	2.82	2.73	2.26	2.12	2.28	2.2	2.5
Exacerbations in previous year	2.8	3	2.7	2.8	3.8	3.5	3.6	>3~	>3~
2 exacerbations in previous year (% patients)	63.3	60	62.9	63.5	38	43	47	46	42
≥3 exacerbations in previous year (% patients)	36.68	40	36.81	36.49	61.86	57.07	52.88	54	57
Never smokers (% patients)	82.2	80.6	78.02$	78.92$#	74$#	73$	70$	80$	78$
OCS use (% patients)	17.8	16.2	10.71$	11.08$#	27$#	25$	23$	30.07$	29.03$
EOS ≥300 cells/µL (% patients)	67.08	65.6	65.6	67.02	43.2	41.3	41.8	56.2	45.16
EOS <300 cells/µL (% patients)	32.9	34.3	34.3	32.9	54.6	55.4	56.5	43.7	54.8
EOS (cells/µl)	369.8	456.5	463.4	490.8	290*	280*	320*	250*	280*
IgE levels	-	-	-	-	149.72*	180.32*	150.12*	-	-
Atopic status	61.3	56.5	61.5	63.0	-	-	-	51.0	52.0
Nasal polyps	23.2	23.2	16.8	18.1	14.4	16.7	17.2	7.0	10.0

The highlighted cells indicate differences across benralizumab and mepolizumab trials.
"Overall" for SIROCCO, MENSA and DREAM refer to a population receiving high-dose ICS. The data in the table represent mean (SD) values unless otherwise indicated. **ACQ-6 in SIROCCO, CALIMA, and DREAM; ACQ-5 in MENSA. $The data are extracted from the respective publications. All other values are extracted from the respective CSR; #Calculated from the reported subgroup data. ~Calculated from the reported frequency of exacerbations; ^Data reported at screening visit; *Geometric means
ACQ: Asthma Control Questionnaire; BENRA: Benralizumab; CSR; Clinical study report; EOS: Eosinophil; FEV1: Forced expiratory volume in one second; FVC: Forced vital capacity; HD: High-dose; ICS: Inhaled corticosteroid; IgE: Immunoglobulin E; IV: Intravenous; MEPO: Mepolizumab; OCS: Oral corticosteroid; PEF: Peak expiratory flow; Q8W: every eight weeks; SD: Standard deviation

Table A4.1 cont'd: Summary of demographic and baseline characteristics for key Phase 3 studies for benralizumab, mepolizumab and reslizumab – ITT Population

Characteristics	SIROCCO		CALIMA		Study 3082		Study 3083		Study 3082 and 3083 (Pooled)	
	High-dose ICS		Medium- to high-dose ICS		Medium- to high-dose ICS		Medium- to high-dose ICS		Medium- to high-dose ICS	
	BENRA Q8W, N=398	Placebo, N=407	BENRA Q8W, N=441	Placebo, N=440	RESLI 3 mg/kg, N=245	Placebo, N=244	RESLI 3 mg/kg, N=232	Placebo, N=232	RESLI 3 mg/kg, N=477	Placebo, N=476
Age, years	47.6	48.7	49.0	48.8	46.6*	46.7*	46.4*	47.5*	-	-
Gender (% males)	36.7	33.9	38.1	40.0	42.0	34.0	38.0	35.0	40.04	34.45
BMI	28.21 (6.18)	28.93 (7.07)	29.0 (6.5)	29.25 (6.54)	27.7 (6.3)	28 (6.2)	27 (5.1)	27 (5.3)	-	-
FEV1 predicted (%)	56.1$	56.6$	57.9	58.0	63.6	65.0	70.4	68.0	-	-
Reversibility (%)	27.2	25.5	24.6	27.3	26.1	26.3	28.1	28.7	-	-
ACQ scores**	2.8	2.87	2.82	2.73	2.66	2.76	2.57	2.61	-	-
Never smokers (% patients)	82.2	80.6	78.9	79.3	-	-	-	-	-	-
OCS use (% patients)	17.8	16.2	10.0	8.9	19.0	19.0	12.0	12.0	-	-
Mean EOS count (cells/µl)	469.8	456.5	465.1	487.5	696.0	624.0	610.0	688.0	-	-
Exacerbation in previous year, mean	2.8	3	2.7	2.8	1.9	2.1	1.9	2.0	-	-
1 exacerbation in previous year	0.0	0.0	0.2	0.0	-	-	-	-	58.07	59.24
2 exacerbations in previous year	63.3	60.0	65.1	65.5	-	-	-	-	18.03	22.48
≥3 exacerbations in previous year	19.8	18.7	21.1	21.1	-	-	-	-	9.22	7.56
≥4 exacerbations in previous year	16.9	21.3	13.6	13.4	-	-	-	-	14.05	10.08
Omalizumab use (% patients)	7.0	7.6	2.7	3.8	-	-	-	-	-	-
Nasal polyps (% patients)	23.2	23.2	16.8	18.1	-	-	-	-	-	-

Highlighted cells indicate differences across benralizumab and reslizumab studies. $Data are extracted from respective publications. All other values for BENRA trials are extracted from respective CSRs.*Extracted from RESLI NICE STA; All other data for RESLI trials are extracted from respective publications. **ACQ-5 in BENRA trials and ACQ-7 in RESLI trials.
ACQ; Asthma Control Questionnaire; BENRA: Benralizumab; BMI; Body Mass Index; CSR; Clinical study report; EOS: Eosinophil; FEV1: Forced Expiratory Volume in one second; ICS; Inhaled Corticosteroid; NICE: National Institute for Health and Care Excellence; OCS: Oral corticosteroid; RESLI: Reslizumab; STA: Single Technology Appraisal; Q8W: every eight weeks

c) **Efficacy and safety data, by trial, for outcomes in scope for the specified subgroup including where this information is not available.**

Please see tables for mepolizumab provided for question A11 below. The key endpoint used in the ITC, rate of exacerbations, has been provided for MUSCA, MENSA and DREAM studies, by individual study and grouped by dose of mepolizumab.

A5. Given that the focus of the submission is stated to be: "patients with a blood eosinophil count of ≥400 cells per microlitre and who have had ≥3 severe asthma exacerbations in the previous 12 months group." Please provide the following for: (i) patients with a blood eosinophil count of ≥400 cells per microlitre; (ii) patients with a blood eosinophil count of ≥400 cells per microlitre who have had ≥3 severe asthma exacerbations in the previous 12 months; and, (iii) patients with a blood eosinophil count of ≥400 cells per microlitre who have had ≥4 severe asthma exacerbations in the previous 12 months groups or provide rationale for omissions where information is not available:

a) **Study selection criteria and process for studies reporting data for the subgroup of interest (list of included studies and rationale for any exclusions per the specified criteria)**

b) **Baseline demographics and clinical characteristics for the specified subgroup in each included trial.**

c) **Efficacy and safety data, by trial, for outcomes in scope for the specified subgroup including where this information is not available.**

Mepolizumab

Please see tables for mepolizumab provided for question A11 below. Demographic and baseline characteristic data have been provided for MUSCA, MENSA and DREAM studies, grouped by dose of mepolizumab for the subgroup of patients with a blood eosinophil count of ≥400 cells per microlitre who have had ≥3 severe asthma exacerbations in the previous 12 months. The key endpoint used in the ITC, rate of exacerbations, has been provided for MUSCA, MENSA and DREAM studies, by individual study and grouped by dose of mepolizumab.

Reslizumab

Having reviewed the NICE committee documents for the reslizumab appraisal (TA479), it is not possible to present any baseline or efficacy data specifically for this subgroup for reslizumab as the relevant data are either not available or have been redacted. However, we have provided the table in the additional results Section of the ITC which presents an indirect comparison of mepolizumab with reslizumab for patients with a blood eosinophil count of ≥400 cells per microlitre who have had ≥4 severe asthma exacerbations in the previous 12 months.

A6. In Section B.3.12 the following statement was made: "There are no ongoing studies for mepolizumab, reslizumab or benralizumab that are relevant for this submission." However, there appear to be no searches for ongoing trials reported in the submission document or related appendices. Please clarify whether searches for ongoing trials were conducted in support of this statement.

A search of the NIH US National Library of Medicine (clinicaltrials.gov) was performed on 25 June 2020 to identify ongoing studies (as of January 2020) for mepolizumab, reslizumab or benralizumab, relevant to this submission. Results were cross-checked using the EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/)

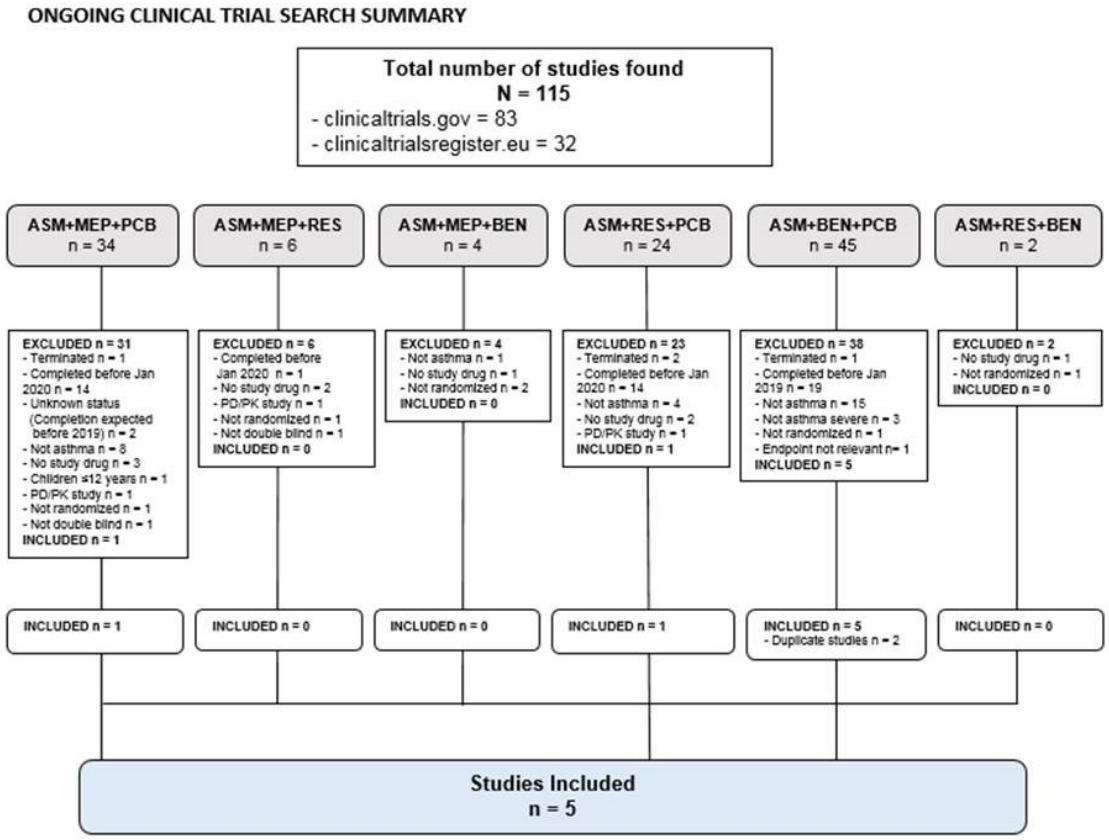
Search terms for clinicaltrials.gov

Search	***Status***	***Condition and Disease***	***Search terms***
#1	All studies	Asthma	[mepolizumab OR bosatria] AND placebo
#2	All studies	Asthma	[reslizumab OR cinquil] AND placebo
#3	All studies	Asthma	benralizumab AND placebo
#4	All studies	Asthma	[mepolizumab OR bosatria] AND [reslizumab OR conquil]
#5	All studies	Asthma	[mepolizumab OR bosatria] AND benralizumab
#6	All studies	Asthma	benralizumab AND [reslizumab OR conquil]

Search terms for the EU Clinical Trials Register

Search	*Search terms*
#1	Asthma AND [mepolizumab OR bosatria] AND placebo
#2	Asthma AND [reslizumab OR cinquil] AND placebo
#3	Asthma AND benralizumab AND placebo
#4	Asthma AND [mepolizumab OR bosatria] AND [reslizumab OR conquil]
#5	Asthma AND [mepolizumab OR bosatria] AND benralizumab
#6	Asthma AND benralizumab AND [reslizumab OR conquil]

Eligibility of trials was assessed by an independent researcher, based on the prespecified PICOS and inclusion and exclusion criteria (see Table 66) as appropriate based on the available information for the trial. The search summary is presented in the figure below:



Asthma AND mepolizumab AND placebo

- A Randomized, Double Blind, Parallel Group Study of the Efficacy and Safety of Mepolizumab as Adjunctive Therapy in Patients With Severe Asthma With Eosinophilic Inflammation [A Safety and Efficacy Study of Mepolizumab in Subjects With Severe Asthma] [https://apps.who.int/trialsearch/Trial2.aspx?TrialID=NCT03562195]

Asthma AND reslizumab AND placebo

- Effect of Reslizumab on small airways in asthma. RESSAPEA [https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-003958-16/NL]

Asthma AND benralizumab AND placebo

- A Multicenter, Randomized, Double-blind, Parallel Group, Placebo Controlled, Phase 3b Study to Evaluate the Safety and Efficacy of Benralizumab 30 mg sc in Patients With Severe Asthma Uncontrolled on Standard of Care Treatment [https://clinicaltrials.gov/ct2/show/NCT03170271] [https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-001040-35/GB]
- A Multicentre, Randomised, Double-blind, Parallel Group, Placebocontrolled, Phase 3 Efficacy and Safety Study of Benralizumab (MED-563) Added to Medium to High-dose Inhaled Corticosteroid Plus Long-acting β2 Agonist in Patients With Uncontrolled Asthma.[Efficacy and Safety Study of Benralizumab in Patients With Uncontrolled Asthma on Medium to High Dose Inhaled Corticosteroid Plus LABA (MIRACLE)] NCT03186209
- A Phase 4, Multicenter, Randomized, Double-blind, Parallel Group, Placebo Controlled Study to Evaluate the Effect of Benralizumab on Structural and Lung Function Changes in Severe Eosinophilic Asthmatics. [Benralizumab Airway Remodeling Study in Severe Eosinophilic Asthmatics] NCT03953300 [https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-003391-13/SE]

A total of 5 trials were identified as ongoing as of January 2020. Details of all these trials are provided in Appendix 1 of this document.

A7. Please clarify the rationale for the selection of trials included in the ITC. For example, in Section B.3.2.1 it is stated that the SIRIUS and DREAM studies were not included in the ITC because of the differences in design and endpoints. However, as DREAM assessed bioequivalent doses, the ERG considered this should have been included (it has also been repeatedly used in previous similar studies). Please provide the results for the analyses including DREAM.

Studies eligible for inclusion in this ITC were required to meet a predefined Population, Intervention, Comparator, Outcomes, Study Design (PICOS) framework. The populations consisted of patients with SEA aged 12 years or greater. Only those assessing approved doses or formulations of licensed anti–IL-5 pathway–directed treatments were included as this represents clinical practice in the United Kingdom.

The SIRIUS trial was designed to demonstrate the efficacy and safety of mepolizumab in reducing OCS dose in severe asthma patients dependent on maintenance OCS. The primary endpoint for the ZONDA study was reduction in OCS use. The study designs and endpoints prevent inclusion of the OCS-reduction studies as part of the ITC. However, a summary of efficacy and safety results from ZONDA and SIRIUS were included in Section B.3.3 for completeness.

In order to provide reassurance that excluding the mepolizumab 75mg IV data from the ITC does not have an impact on the results and interpretation, we have provided a meta-analysis of the trial data for mepolizumab in Question A11 to demonstrate consistency in the results for mepolizumab when the IV dose is included and excluded.

A8. Please clarify which studies informed each subgroup analysis for each outcome presented, and where pooled estimates from the two additional studies (Fitzgerald, 2018; Brusselle, 2017) identified were used. Please provide or adapt Table 40 in the CS for each outcome and subgroup.

The studies included in each subgroup in the ITC are described in the table below.

Table A8.1 Studies included in the Indirect Treatment Comparison

>=400 cells/uL			
Endpoint	**Mepolizumab**	**Benralizumab**	**Reslizumab**
Clinically significant exacerbations	MENSA MUSCA	Fitzgerald 2018 (SIROCCO + CALIMA)	3082 and 3083
ACQ		Fitzgerald 2018 (SIROCCO + CALIMA)	NCT00587288 3081, 3082, 3083 , 3084
Exacerbations requiring ED visit/hospitalisation		N/A	Brusselle 2017 (Studies 3082 + 3083)
FEV1		Fitzgerald 2018 (SIROCCO + CALIMA,)	NCT00587288 3081, 3082, 3083 , 3084
>=300 cells/uL			
Endpoint	**Mepolizumab**	**Benralizumab**	**Reslizumab**
Clinically significant exacerbations	MENSA MUSCA	SIROCCO CALIMA	N/A
ACQ			
Exacerbations requiring ED visit/hospitalisation			
FEV1			
>=150 cells/uL			
Endpoint	**Mepolizumab**	**Benralizumab**	**Reslizumab**
Clinically significant exacerbations	MENSA MUSCA	Fitzgerald 2018 (SIROCCO + CALIMA)	N/A
ACQ			
FEV1			
ITT			
Endpoint	**Mepolizumab**	**Benralizumab**	**Reslizumab**
Clinically significant exacerbations	MENSA MUSCA	SIROCCO CALIMA	3082 and 3083
ACQ			NCT00587288 3081, 3082, 3083 , 3084
Exacerbations requiring ED visit/hospitalisation			Brusselle 2017 (3082 + 3083)
FEV1			NCT00587288 3081, 3082, 3083 , 3084

A9. Please clarify how many patients were included in each subgroup and each outcome of the ITC analysis, by treatment vs comparator contrast.

The number of patients included in each subgroup from each trial for the analyses of exacerbation rate are described in the table below. All patients for each study would have been included in the analysis of this parameter.

For the other endpoints, ACQ, and FEV_1 the numbers of patients included are likely to be very similar and will only be slightly reduced if the baseline value for that particular endpoint was missing.

Table A9.1 Number of patients in each study included in the ITP

>=400 cells/uL			
Endpoint	**Mepolizumab**	**Benralizumab**	**Reslizumab**
Clinically significant exacerbations	MENSA (N=173) MUSCA (N=182)	Fitzgerald 2018 (SIROCCO + CALIMA, N=604)	Study 3082 (N=489) Study 3083 (N=464)
ACQ		Fitzgerald 2018 (SIROCCO + CALIMA, N=604)	NCT00587288 (N=106) Study 3081 (N=211) Study 3082 (N=489) Study 3083 (N=464) Study 3084 (N=96)
Exacerbations requiring ED visit/hospitalisation		N/A	Brusselle 2017 (Study 3082 + Study 3083, N=953)
FEV1		Fitzgerald 2018 (SIROCCO + CALIMA, N=604)	NCT00587288 (N=106) Study 3081 (N=211) Study 3082 (N=489) Study 3083 (N=464) Study 3084 (N=96)
>=300 cells/uL			
Endpoint	**Mepolizumab**	**Benralizumab**	**Reslizumab**
Clinically significant exacerbations	MENSA (N=226) MUSCA (N=242)	SIROCCO (N=534) CALIMA (N=487)	N/A
ACQ			
Exacerbations requiring ED visit/hospitalisation			
FEV1			
>=150 cells/uL			
Endpoint	**Mepolizumab**	**Benralizumab**	**Reslizumab**
Clinically significant exacerbations	MENSA (N=322)		N/A

ACQ	MUSCA (N=336)	Fitzgerald 2018 (SIROCCO + CALIMA, N=1294)	
FEV1			
ITT			
Endpoint	**Mepolizumab**	**Benralizumab**	**Reslizumab**
Clinically significant exacerbations	MENSA (N=576) MUSCA (N=551)	SIROCCO (N=805) CALIMA (N=881)	Study 3082 (N=489) Study 3083 (N=464)
ACQ			NCT00587288 (N=106) Study 3081 (N=211) Study 3082 (N=489) Study 3083 (N=464) Study 3084 (N=96)
Exacerbations requiring ED visit/hospitalisation			Brusselle 2017 (Study 3082 + Study 3083, N=953)
FEV1			NCT00587288 (N=106) Study 3081 (N=211) Study 3082 (N=489) Study 3083 (N=464) Study 3084 (N=96)

A10. Please clarify if the indirect treatment comparison was undertaken using a two-step method (meta-analyse by subgroup and contrast and then subtract) or a one-step method (i.e. a meta-regression-based method).

Indirect treatment effect estimates were produced by using the two-step, Bucher method.

A11. Please present pairwise meta-analyses of direct evidence for each subgroup and outcome reported that is relevant to this appraisal:

- patients with a blood eosinophil count of ≥150 cells per microlitre or greater
- patients with a blood eosinophil count of ≥300 cells per microlitre or greater
- **PRIORITY** patients with a blood eosinophil count of ≥300 cells per microlitre who have had ≥3 severe asthma exacerbations in the previous 12 months;
- **PRIORITY** patients with a blood eosinophil count of ≥300 cells per microlitre who have had ≥4 severe asthma exacerbations in the previous 12 months;

- **PRIORITY** patients with a blood eosinophil count of ≥400 cells per microlitre who have had ≥3 severe asthma exacerbations in the previous 12 months;

- **PRIORITY** patients with a blood eosinophil count of ≥400 cells per microlitre who have had ≥4 severe asthma exacerbations in the previous 12 months

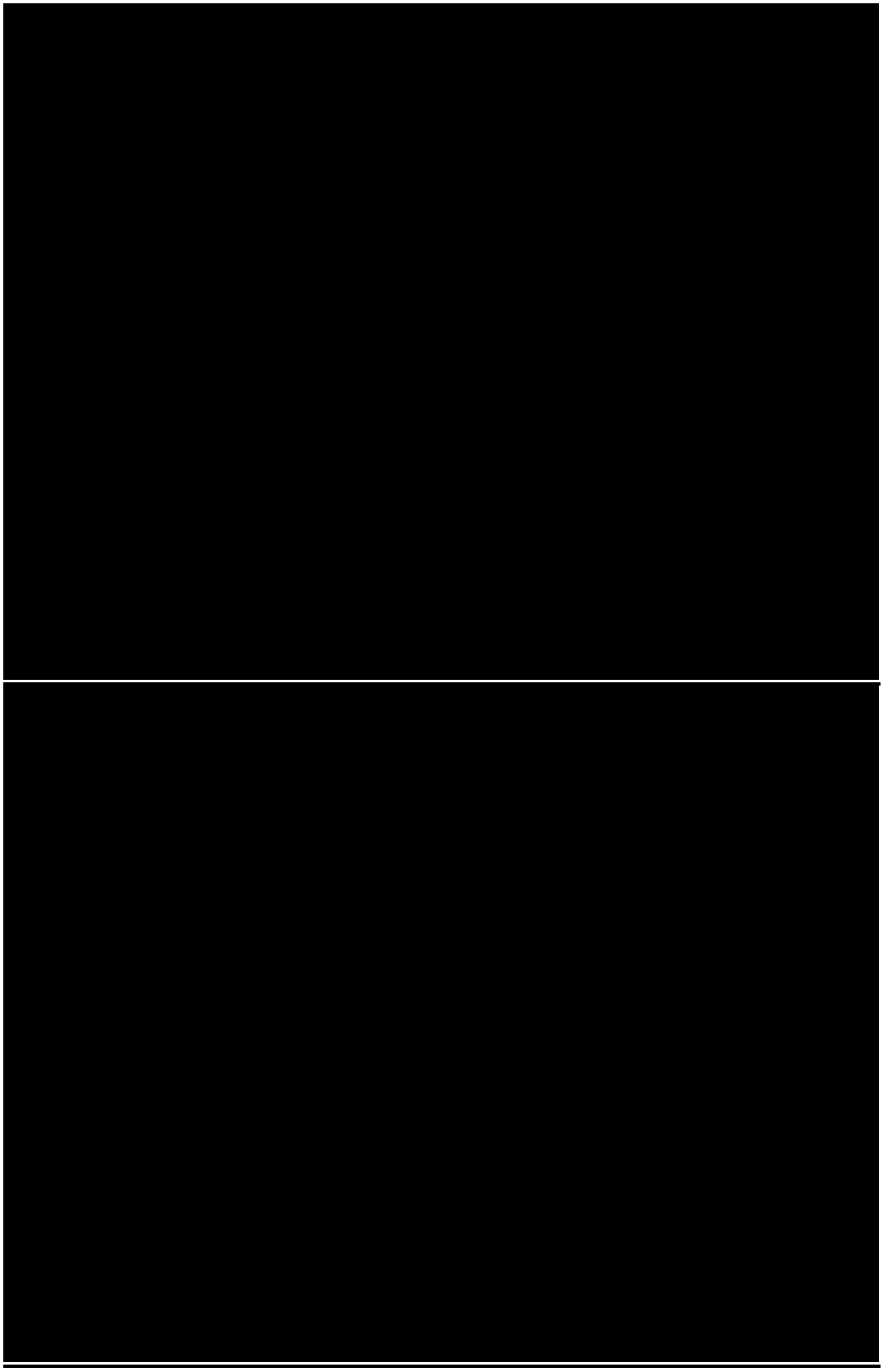
We have provided data in the following subgroups that are most relevant to the decision problem for this submission: i) patients with a blood eosinophil count of ≥300 cells per microlitre who have had ≥4 severe asthma exacerbations in the previous 12 months, and ii) patients with a blood eosinophil count of ≥400 cells per microlitre who have had ≥3 severe asthma exacerbations in the previous 12 months.

i) Blood eosinophil count of ≥300 cells per microlitre who have had ≥4 severe asthma exacerbations in the previous 12 months

Baseline demographics and clinical characteristics

As efficacy data are provided for i) the study treatment arms for the SC 100mg dose only (for the two studies MUSCA and MENSA) and ii) the treatment arms of 100mg SC dose combined with the 75mg IV dose (for the three studies MUSCA, MENSA and DREAM) baseline data for these groups are provided below to demonstrate that baseline demographics and clinical characteristics are comparable irrespective of whether or not the IV dose is included in the analyses.

Table A11.1: Baseline demographics and clinical characteristics



Efficacy Data

Please note due to time and resource limitations we have restricted the efficacy data analyses to the primary parameter of exacerbation rate per year. This was also the key parameter used in the health economic modelling for all anti-IL-5 appraisals.

We have not provided any additional safety information as this was provided for this subgroup as part of TA431. The three anti-IL5s have comparable safety profiles.

In order to assess the impact of not including the DREAM study or the MENSA 75mg treatment arms in the published ITC, the efficacy analyses provided below present i) results when only the 100mg SC dose data are considered and ii) when the 100mg SC dose data are combined with the 75mg IV dose.

The results demonstrate consistency in the degree of benefit demonstrated with mepolizumab compared with placebo on the reduction in exacerbation rate irrespective of whether the 75mg dose study arms are included in the analysis.

Table A11.2: Subgroup Analysis of Clinically Significant Exacerbations

In addition, please see below the ITC results of mepolizumab compared with benralizumab for this subgroup, extracted from the additional results section of the published ITC.

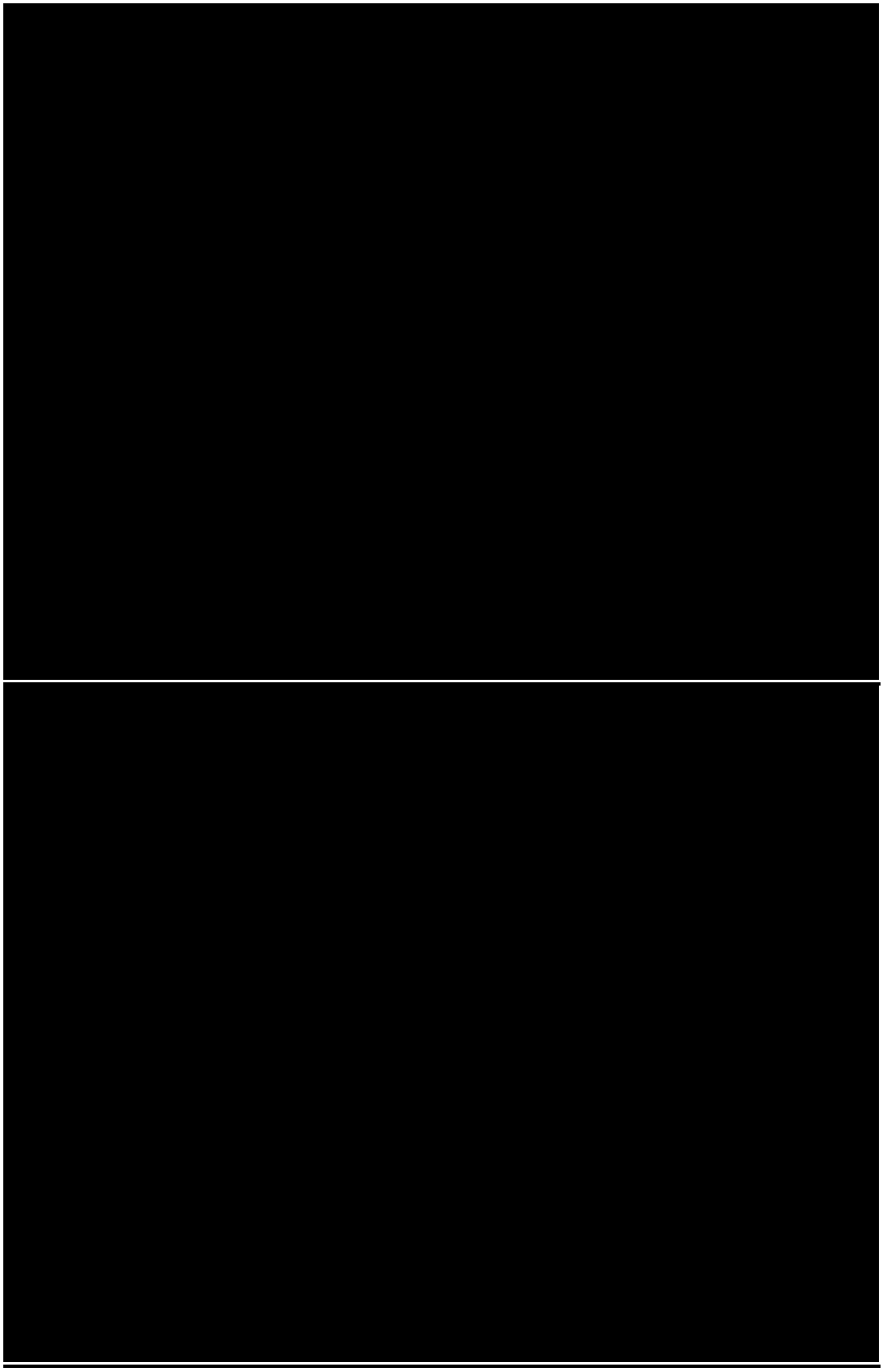
TABLE E10. Treatment comparison on the rate of clinically significant exacerbations by exacerbation history (mepolizumab compared with benralizumab)

	Clinically significant exacerbations, RR (95% CI)	
	≥3 Exacerbations in prior year	≥4 Exacerbations in prior year
MEPO vs PBO	0.28 (0.19-0.41)†	0.23 (0.14-0.37)†
BENRA vs PBO	0.46 (0.35-0.61)†	0.46 (0.31-0.68)†
MEPO vs BENRA	0.61 (0.38-0.99)*	0.50 (0.27-0.94)*

All patients had baseline blood eosinophil counts of 300 cells/μL or greater plus ACQ score of 1.5 or greater.
BENRA, Thirty milligrams of benralizumab Q8W; *MEPO*, 100 mg of mepolizumab administered subcutaneously; *PBO*, placebo.
*$P < .05$ and †$P < .001$.

ii) **Blood eosinophil count of ≥400 cells per microlitre who have had ≥3 severe asthma exacerbations in the previous 12 months**

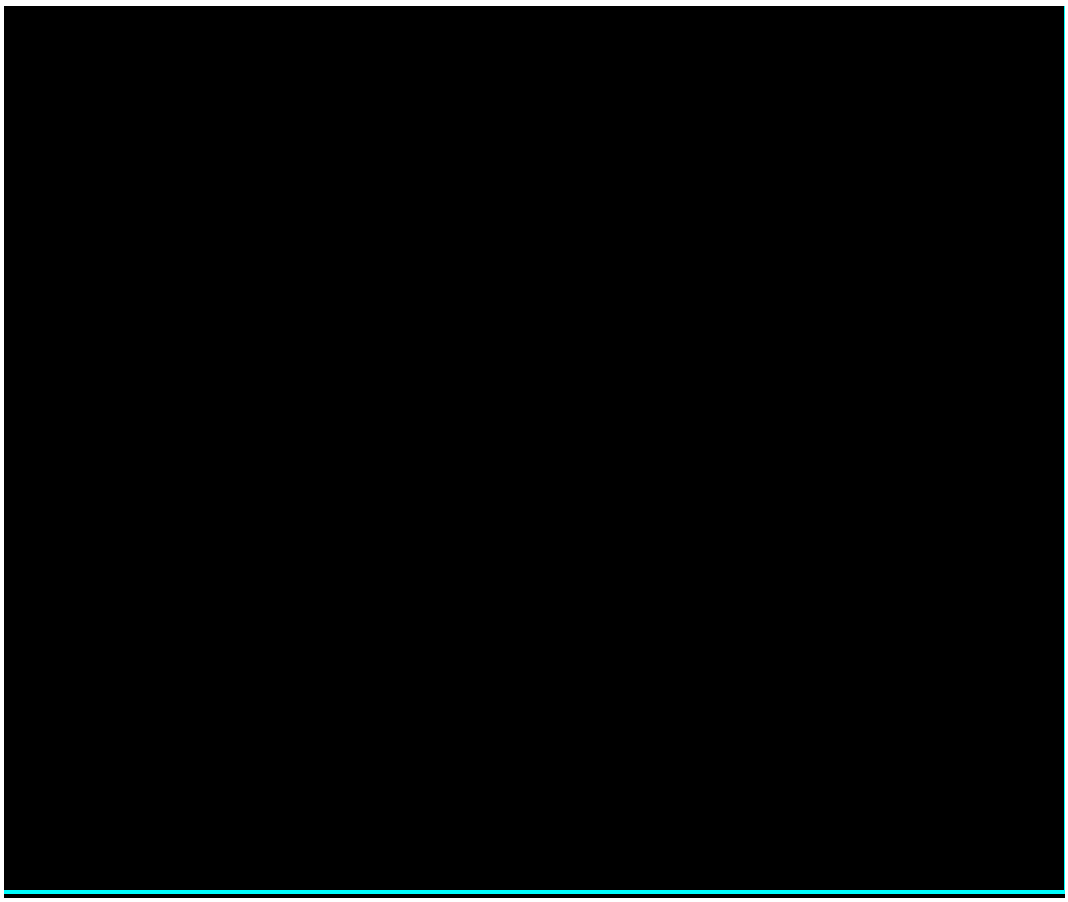
Table A11.3: Baseline demographics and clinical characteristics



Efficacy data

Similar to the results seen for the subgroup comprising patients with blood eosinophil count of ≥300 cells per microlitre who have had ≥4 severe asthma exacerbations in the previous 12 months, the results for this subgroup also demonstrate good consistency in the degree of benefit observed with mepolizumab compared with placebo on the reduction in exacerbation rate irrespective of whether the 75mg dose study arms are included in the analysis.

Table A11.4: Subgroup Analysis of Clinically Significant Exacerbations



Although we did not conduct an analysis of mepolizumab compared with either benralizumab or reslizumab specifically for this subgroup, there was an analysis provided in the ITC publication comparing mepolizumab and reslizumab for a slightly more restricted subgroup comprising patients with a blood eosinophil count of ≥400 cells per microlitre and who have had ≥4 severe asthma exacerbations in the previous 12 months. Please see the results from this analysis in the table extracted from the additional results section of the published ITC below.

TABLE E12. Treatment comparison on the rate of clinically significant exacerbations by exacerbation history (mepolizumab compared with reslizumab)

	Clinically significant exacerbations, RR (95% CI)
	≥4 Exacerbations in prior year
MEPO vs PBO	0.14 (0.07-0.29)†
RESLI vs PBO	0.36 (0.22-0.58)†
MEPO vs RESLI	0.40 (0.17-0.93)*

All patients had baseline blood eosinophil counts of 400 cells/μL or greater plus ACQ scores of 1.5 or greater.
MEPO, 100 mg of mepolizumab administered subcutaneously; *PBO*, placebo; *RESLI*, 3 mg/kg reslizumab.
*$P < .05$ and †$P < .001$.

A12. Please clarify the rationale for the inclusion of only placebo-controlled trials. Was a systematic review undertaken to confirm that there are no trials with relevant comparators (e.g. benralizumab vs reslizumab), but no placebo arms?

The text provided in section E.1.1.3 of the appendices ID3750_Mepolizumab_FTA NICE submission_Appendices_[noACIC] was inaccurate, the systematic literature search conducted on 14 January 2020 did include trials for the comparators. We confirm that no direct comparative trials with reslizumab and benralizumab were identified. The updated text should read:

"For the search conducted in January 2020, eligibility of articles was assessed by an independent researcher, based on the prespecified PICOS and inclusion and exclusion criteria (see Table 66). Selection was firstly based on title and abstract, but where inclusion still remained unclear, full texts were evaluated. The comparators considered for this appraisal were placebo, reslizumab and benralizumab."

Section B: Clarification on cost data

B1. It would be helpful if you could please make the following amendments to the cost comparison and provide updated results for both the base case and sensitivity analyses

- **Assume a unit cost per hour of specialist nurse time to be £113 (based on PSSRU 2019 estimates)**
- **Adjust the price of benralizumab to reflect TA565 guidance i.e. £1,955 (instead of £1,995) per 30 mg injection. Also adjust the annual cost to £15,640 from £15,960.**

Table 1 Base-case results using list prices with a one-year time horizon

Technologies	Acquisition costs (£)	Administration costs (£)	Adverse event costs (£)	Other costs (£)	Total costs (£)
Mepolizumab 100 mg powder for solution for injection	10,920	329.54	NA	NA	11,249.54
Mepolizumab 100 mg solution for injection in pre-filled syringe or pen	10,920	207.21	NA	NA	11,127.21
Mepolizumab 100 mg solution for injection in pre-filled syringe or pen (self-administration)	10,920	113.01	NA	NA	11,033.01
Reslizumab 10 mg/mL concentrate for solution for infusion	14,624.61	1,064.04	NA	NA	15,688.65
Benralizumab 30 mg pre-filled syringe or pen	15,640	160.11	NA	NA	15,800.11
Benralizumab 30 mg pre-filled syringe or pen (self-administration)	15,640	113.01	NA	NA	15,753.01
Abbreviations: NA; not applicable					

Table 2 Base-case results using the mepolizumab PAS price with a one-year time horizon

Technologies	Acquisition costs (£)	Administration costs (£)	Adverse event costs (£)	Other costs (£)	Total costs (£)
Mepolizumab 100 mg powder for solution for injection	[redacted]	329.54	NA	NA	[redacted]
Mepolizumab 100 mg solution for injection in pre-filled syringe or pen	[redacted]	207.21	NA	NA	[redacted]
Mepolizumab 100 mg solution for injection in pre-filled syringe or pen (self-administration)	[redacted]	113.01	NA	NA	[redacted]
Reslizumab 10 mg/mL concentrate for solution for infusion	14,624.61	1064.04	NA	NA	15,688.65
Benralizumab 30 mg pre-filled syringe or pen	15,640	160.11	NA	NA	15,800.11
Benralizumab 30 mg pre-filled syringe or pen (self-administration)	15,640	113.01	NA	NA	15,753.01
Abbreviations: NA; not applicable					

Table 3 Sensitivity analysis of administration costs with 70% of severe asthma patients self-administering

Technologies	Administration costs (£)	Weighting (%)	TOTAL Administration Costs (£)	Total Cost (drug + admin) (£)
Mepolizumab 100 mg powder for solution for injection	329.54	30	177.97	[redacted]
Mepolizumab 100 mg solution for injection in pre-filled syringe or pen (Self-administration)	113.01	70		
Reslizumab 10 mg/mL concentrate for solution for infusion	1,064.04	100	1,064.04	15,688.65
Benralizumab 30 mg pre-filled syringe or pen	160.11	30	127.14	15,767.14
Benralizumab 30 mg pre-filled syringe or pen (Self-administration)	113.01	70		

Table 4 Sensitivity analysis of administration costs with 50% of severe asthma patients self-administering

Technologies	Administration costs (£)	Weighting (%)	Total administration costs (£)	Total Cost (drug + admin) (£)
Mepolizumab 100 mg powder for solution for injection	329.54	50	221.28	[redacted]
Mepolizumab 100 mg solution for injection in pre-filled syringe or pen (self-administration)	113.01	50		
Reslizumab 10 mg/mL concentrate for solution for infusion	1,064.04	100	1,064.04	15,688.65
Benralizumab 30 mg pre-filled syringe or pen	160.11	50	136.56	15,776.56
Benralizumab 30 mg pre-filled syringe or pen (self-administration)	113.01	50		

Table 5 Sensitivity analysis of administration costs with 25% of severe asthma patients self-administering

Technologies	Administration costs (£)	Weighting (%)	Total administration costs (£)	Total Cost (drug + admin)
Mepolizumab 100 mg powder for solution for injection	329.54	75	275.41	[redacted]
Mepolizumab 100 mg solution for injection in pre-filled syringe or pen (self-administration)	113.01	25		
Reslizumab 10 mg/mL concentrate for solution for infusion	1,064.04	100	1,064.04	15,688.65
Benralizumab 30 mg pre-filled syringe or pen	160.11	75	148.34	15,788.34
Benralizumab 30 mg pre-filled syringe or pen (self-administration)	113.01	25		

B2. In Table 56 (on page 146) it is stated that the number of units required for one year of treatment with mepolizumab 100mg (solution for injection with pre-filled syringe) is 8. This appears to be an error. Could you please confirm that this should be 13.

Yes, we can confirm that the number of units required for one year of treatment with mepolizumab 100mg (solution for injection in pre-filled syringe or pen) is 13.

B3. In Table 57 (on page 147), one of the source references for reslizumab 10 mg/mL concentrate for solution for infusion is noted to be TA79. This appears to be an error. Can you please confirm this should be TA479?

We can confirm that the source references for reslizumab 10 mg/mL concentrate for solution for infusion should be TA479.

B4. In Table (57 on page 147), the administration cost of subsequent reslizumab doses is estimated to be £66.67 based on a 10-minute administration time assumption. 10 minutes, appears to be an error. Could you please confirm that the administration time should have been 40 minutes?

We can confirm that this should be 40 minutes of administration time for subsequent reslizumab doses.

Section C: Textual clarification and additional points

C1. The company has submitted a cost comparison of mepolizumab compared with benralizumab and reslizumab. Given the comparators do not have a licence for a paediatric population, can the company please clarify whether the adult population is the only population being considered in their cost comparison or is the company proposing to expand any recommendation for mepolizumab to include a paediatric population, in line with the marketing authorisation for mepolizumab?

This FTA submission only covers the adult population for the cost comparison as the comparators are currently recommended for the adult population only.

APPENDIX 1

Details of ongoing studies for mepolizumab, benralizumab and reslizumab

MEPOLIZUMAB	
Study title	A Safety and Efficacy Study of Mepolizumab in Subjects With Severe Asthma
Study identifier	NCT03562195
Sponsor	GlaxoSmithKline
Study locations	China
Study status	Recruiting
Study start date	29 August 2018
Estimated primary completion date	30 November, 2022
Study design	Multicentre, randomized, double-blind, parallel group. Maximum duration 56 weeks
Study phase	Phase 3
Population	300 subjects, ≥12 years with severe eosinophilic asthma
Intervention(s)	SC mepolizumab 100 mg with rescue medication Salbutamol MDI as needed
Comparator(s)	Placebo with rescue medication Salbutamol MDI as needed
Primary outcome measures	Number of clinically significant exacerbations of asthma up to 52 weeks
Other assessed outcomes	• Time to first clinically significant exacerbation • Mean change in baseline SGRQ • Number of exacerbations requiring hospitalization or ED visits • Mean change in baseline FEV1 at Week 52 • Adverse events • Haematology parameters • Abnormal SBP/DBP/pulse/ECG • Changes from baseline in blood eosinophil counts • Immunogenicity
Abbreviations: DMP: diastolic blood pressure; ECG: echocardiogram; ED: emergency department; FEV: forced expiratory volume; SBP: systolic blood pressure; SGRQ: St George's Respiratory Questionnaire	

RESLIZUMAB	
Study title	Effect of Reslizumab on small airways in asthma. RESSAPEA
Study identifier	EudraCT number: 2017-003958-16
Sponsor	Non-commercial, University of Amsterdam
Study locations	Academic Medical Center, University of Amsterdam
Study status	Ongoing
Study start date	10 August 2018
Actual primary completion date	Estimated duration 3 years
Study design	Single-centre, randomized, placebo-controlled, double-blind, parallel group study
Study phase	Phase 4
Population	33 subjects ≥18 years with severe eosinophilic asthma
Intervention(s)	IV reslizumab
Comparator(s)	Placebo
Primary outcome measures	• Change from baseline in regional image based hyperinflation (iVlobes) and in (specific) iVAw after 3 months reslizumab treatment compared to changes in the placebo group (timepoints: baseline and 12 weeks)
Other assessed outcomes	• (specific) iRaw, exploratory parameters from FRI, iVlung, air trapping specific imaged-based airway volume (s)iVaw at TLC, internal lobar airflow distribution, low attenuation or emphysema score, blood vessel density, airway wall thickness and aerosol deposition concentrations • Correlations between changes in HRCT parameters and SGRQ, AQLQ, ACQ, FEV1/FVC, FVC, FRC, RV/TLC, FeNO and cell differential counts in sputum and blood
Abbreviations: ACQ: asthma control questionnaire; AQLQ: asthma quality of life questionnaire; FeNO: fractional exhaled nitric oxide; FEV: forced expiratory volume; FRC: functional residual capacity; FVC: forced vital capacity; RV/TLC: residual volume/total lunch capacity	

BENRALIZUMAB	
Study title	A Study of the Safety and Effectiveness of Benralizumab to Treat Patients With Severe Uncontrolled Asthma (ANDHI)
Study identifier	NCT03170271
Sponsor	AstraZeneca
Study locations	USA
Study status	Active, not recruiting
Study start date	7 July 2017
Estimated primary completion date	25 September 2019
Study design	Multicentre, randomized, double-blind, parallel group, placebo-controlled for 24 weeks. After 24-weeks, eligible patients may enter a 56 week open label period
Study phase	Phase 3b
Population	659 patients aged 18–75 years
Intervention(s)	SC 30mg benralizumab
Comparator(s)	SC placebo
Primary outcome measures	Rate of asthma exacerbations 24 weeks after start of dosing, and the annualised rate of asthmas exacerbations
Other assessed outcomes	• Change in baseline SGRQ • Adapted GINA step category changes • Change in continuous asthmas efficacy measures (SGRQ and ACQ6) • Number of clinically significant asthma exacerbations
Abbreviations: ACQ6: asthma control questionnaire; GINA: Global Initiative for Asthma; SC: subcutaneous; SGRQ: St George's Respiratory Questionnaire	

BENRALIZUMAB	
Study title	Efficacy and Safety Study of Benralizumab in Patients With Uncontrolled Asthma on Medium to High Dose Inhaled Corticosteroid Plus LABA (MIRACLE)
Study identifier	NCT03186209
Sponsor	AstraZeneca
Study locations	76 sites in China, Korea, Taiwan, Philippines
Study status	Recruiting
Study start date	7 September 2017
Estimated primary completion date	1 February 2023
Study design	Multicentre, randomized, double-blind, parallel group, placebo-controlled. Maximum duration 48 weeks
Study phase	Phase 3
Population	Estimated 666 Chinese subjects, 12–75 years with uncontrolled asthma
Intervention(s)	SC benralizumab with rescue medication medium to high-dose inhaled corticosteroid plus long-acting β agonist
Comparator(s)	SC placebo with rescue medication medium to high-dose inhaled corticosteroid plus long-acting β agonist
Primary outcome measures	Annual asthma exacerbation rate over the 48 week treatment period
Other assessed outcomes	• Time to first clinically significant exacerbation • Change in baseline asthma symptom score at Week 48 • Change in baseline SGRQ • Number of exacerbations requiring hospitalization or ED visits • Change in baseline FEV1 at Week 48 • Change in baseline ACQ6 at Week 48 • Adverse events • Haematology parameters • Abnormal SMP/DBP/pulse/ECG • Changes from baseline in blood eosinophil counts • Change in rescue medication • Immunogenicity • Home lung function assessment based on morning/evening PEF • Proportion of night awakening due to asthma
Abbreviations: ACQ6: asthma control questionnaire; ECG: echocardiogram; DBP: diastolic blood pressure; ED: emergency department; FEV: forced expiratory volume; PEF: peak flow test; SBP: systolic blood pressure; SC: subcutaneous; SGRQ: St George's Respiratory Questionnaire	

BENRALIZUMAB	
Study title	Benralizumab Airway Remodelling Study in Severe Eosinophilic Asthmatics (CHINOOK)
Study identifier	NCT03953300
Sponsor	AstraZeneca
Study locations	USA, UK, Canada, Denmark, Sweden
Study status	Recruiting
Study start date	8 October 2019
Estimated primary completion date	10 August 2022
Study design	Multicentre, randomized, double-blind, parallel group, placebo-controlled study. Maximum duration 48 weeks
Study phase	Phase 4
Population	Estimated 81 subjects, 18–65 years with severe eosinophilic asthma
Intervention(s)	SC 30 mg benralizumab with rescue medication medium to high-dose inhaled corticosteroid plus long-acting β agonist
Comparator(s)	SC placebo with rescue medication medium to high-dose inhaled corticosteroid plus long-acting β agonist
Primary outcome measures	• Change in eosinophil numbers in submucosa measured by MBP staining in endobronchial biopsies from baseline to Week 48 • Change in airway wall area percentage as the overall median for airway generations 3 and 4 combined as measured by quantitative tomography imaging from baseline to Week 48
Other assessed outcomes	• Change in air trapping of the lung • Change in airway lumen volume and airway resistance • Change in endobronchial biopsies on airway epithelial cell integrity, reticular basement membrane, vascularization of the sub-mucosa, airway smooth muscle mass percentage, mucin RAC • Absolute change in peripheral airway resistance • Absolute change in pre-bronchodilator whole body plethysmography and FEV1/FVC measures • Adverse events
Abbreviations: FVC: forced vital capacity; FEV: forced expiratory volume; MBP: major basic protein; RAC: respiratory assessment criteria; SC: subcutaneous	

NICE National Institute for Health and Care Excellence

Patient organisation submission

Review of NICE Technology Appraisal Guidance TA431: mepolizumab for treating severe eosinophilic asthma ID3750

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
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Asthma UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Every 10 seconds someone has a potentially life-threatening asthma attack and three people die every day. Tragically the majority of these could be prevented, whilst others suffer with asthma so severe current treatments don't work. This must change. That's why Asthma UK exists. We work to stop asthma attacks and, ultimately cure asthma by funding world leading research and scientists, campaigning for improved care and supporting people with asthma to reduce their risk of a potentially life-threatening asthma attack. Stop asthma attacks. Cure asthma. Asthma UK has now merged with the British Lung Foundation to form the British Lung Foundation Partnership and no longer has a membership base.
4b. 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.]	Asthma UK has not received any industry funding. However, Asthma UK has recently merged with the British Lung Foundation (to form the Asthma UK & British Lung Foundation Partnership). The following funding is confidential. The British Lung Foundation has previously received the following funding from the relevant manufacturers as set out in the final stakeholder list for the Taskforce for Lung Health: • AstraZeneca - £35K in FY 18/19 for Taskforce Year 2 funding, £45k in FY 19/20 for Taskforce Year 3 funding • GSK - £45k in FY 18/19 for Taskforce Year 2 funding, £45k in FY 19/20 for Taskforce Year 3 funding The British Lung Foundation also received the following funding from the relevant manufacturers for other projects:

If so, please state the name of manufacturer, amount, and purpose of funding.	FY 2018/19 • GSK – 3,000 for a COPD parliamentary reception • GSK - £400 for patient advocacy meetings • GSK - £3,500 for a parliamentary event in Scotland • GSK - £2,000 for ARNS Conference support for 10 places FY 2019/20 • GSK - £2,500 for a Welsh parliamentary reception for World COPD Day **None of the above funding has been used for Asthma UK's severe asthma policy work.**
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?	Information about the experiences of patients and carers living with asthma is gathered regularly through our helpline, email and social media interactions with people with asthma. Asthma UK also conducts patient surveys, focus groups and qualitative interviews.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Asthma is one of the most prevalent long-term conditions in the UK, with 5.4 million people currently receiving treatment for the condition. On average, 3 people die from an asthma attack in the UK every day[1] and more than 1400 people died from an asthma attack in England and Wales in 2018 [2]. Severe asthma affects around 3.6% of people with asthma – which equates to around 173,000 people in England and Wales.[3] The National Review of Asthma Deaths highlighted that almost 40% of asthma deaths were patients who had severe asthma.[4] Severe asthma does not respond well to standard treatments and requires more intensive therapies with significant side effects to control symptoms and prevent asthma attacks, hospitalisations and deaths. People with severe asthma fall outside the robust evidence-base that informs most asthma care, requiring specialist treatment and pathways. Until the recent NICE COVID-19 rapid severe asthma guideline, there had been no dedicated NICE guideline for treating severe asthma. Ongoing severe symptoms and a complex medicines regime are often accompanied by frequent hospital admissions for many people with severe asthma. Numerous hospital admissions can lead to further social isolation and economic disadvantage, as well as high costs for the NHS.[5] As such, people with uncontrolled severe asthma cost four times as much to treat as the average patient.[6] What is more, people with severe asthma remain symptomatic on high doses of treatment. However, a lack of referrals to a specialist for an

[1] Asthma UK, Asthma Facts and Statistics, accessed at: https://www.asthma.org.uk/about/media/facts-and-statistics/ (July 2019)
[2] Office for National Statistics, Deaths Registered in England and Wales 2018. Accessed at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsregistrationsummarytables/2018, (July 2019).
[3] Hekking P, et al, 'The prevalence of severe refractory asthma', The Journal of Allergy and Clinical Immunology, 135(4), (2015)
[4] Royal College of Physicians, 2014, 'Why asthma still kills: the National Review of Asthma Deaths (NRAD)', accessed at https://www.rcplondon.ac.uk/file/868/download?token=JQzyNWUs
[5] D'Amato, Gennaro, et al., "Treating severe allergic asthma with anti-IgE monoclonal antibody (Omalizumab): a review." *Multidisciplinary respiratory medicine* 9.1 (2014): 23.
[6] Marjan Kerkhof et al., 'Healthcare Resource Use and Costs of Severe, Uncontrolled Eosinophilic Asthma in the UK General Population', Thorax (2017), https://doi.org/10.1136/thoraxjnl-2017-210531

assessment often leads to patients being left on continuous courses of oral steroids.[7] Oral steroids are known to cause toxic or debilitating side effects including mood-swings, anxiety, increased appetite, diabetes, cataracts and osteoporosis.

Experiences of people living with severe asthma

Our forthcoming report 'Falling into isolation: Lived experience of people with severe asthma'[8] highlights through qualitative interviews the experiences of six adults with severe asthma. The interviews reiterated that living with severe asthma is so much more than asthma attacks and occasional hospital admissions. It can have devastating consequences on every aspect of people's lives. They may feel isolated, lonely and scared, left without hope or the right support. For example:

"But, obviously, I spent all the time in hospital. The first few times you get admitted, everybody comes to see you. But then, it gets a little bit boring and out of the way. So, friendships drift off and fall into a bit of isolation, really." (Participant 2)

"I just wish I had been put on this biologic a lot sooner. Because the period I was suffering, you can't explain it in words. It was really, really hard for me. It was just so depressing that sometimes you think your life is just not worth living anymore." (Participant 1)

"*They were just saying to my husband well, we've tried everything and she's not responding. And all I could remember was the clock on the wall and I was just staring at the clock, thinking that when am I going to stop breathing because it's getting too painful, I just can't carry on anymore. And that experience, I think, is still stuck with me every time I can't breathe. It just brings all that back to me. And I think that's part of my panic and I just start breathing, getting anxiety."* (Participant 1)

We also found that severe asthma can have a huge impact on work or school. For example:

[7] Asthma UK, 'Slipping through the net: The reality facing patients with difficult and severe asthma', (2018), Accessed at: https://www.asthma.org.uk/globalassets/get-involved/external-affairs-campaigns/publications/severe-asthma-report/auk-severe-asthma-gh-final.pdf p.8

[8] Lottie Renwick, Asthma UK, 'Falling into isolation: Lived experience of people with severe asthma' (2020) Not yet published

	"Yes, and the worst thing was trying to get used to it, from being such an active person and working fulltime, it was just trying to get used to it because I just couldn't work. For quite a long time, I just couldn't work" (Participant 1) *"I've been off work, most of the time this year because of my asthma. I've literally had no life, really. And then when I was in Year 11, my school attendance was 43%."* (Participant 5) "*And then I knew it was serious when I retired from my job at the age of 30, because I was spending more time as a patient than I was as a nurse."* (Participant 6) Previous research Asthma UK has conducted found that even across the far broader asthma population, 20% of people aged 0-59 miss 1-4 days of work or education a year due to their asthma, whilst 19% miss 10 or more days.[9] We also know from these interviews severe asthma can create a huge burden on family members and carers. For example: *"I think it was a big relief [the severe asthma diagnosis] for my parents as well, because I think they felt the burden as well. Because they had to stop work to look after me. So, obviously, they had the financial burden. I think that they felt that they were labelled as well, because I was still poorly despite them helping me administer my medication and things. Even though it was asthma, it was a separate asthma condition*" (Participant 2).

[9] Asthma UK, 'Annual Asthma Survey 2016 report', 2017, p.31, Accessed at: https://www.asthma.org.uk/share/?rid=6770

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Oral corticosteroids (OCS) The existing treatments for severe asthma are extremely limited. Patients predominantly rely on OCS to control their symptoms, which can cause toxic and debilitating side effects, particularly when taken for long periods, which in cases of severe asthma, they often are. A survey into the side effects of OCS used by people with asthma was conducted by Asthma UK in 2017. Various side effects were reported, including 56% reporting weight gain; 37% felt more anxious and 33% reported aching and cramping muscles and joints.[10] NHS England reports that the side-effects of maintenance OCS, which "will affect the majority of patients with severe asthma" include diabetes, hypertension, cataracts, osteoporosis, glaucoma, skin disease, reflux oesophagitis, non-alcoholic fatty liver disease and obesity.[11] Likewise, a study by Sweeney et al. which presents data from two large severe asthma populations (the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry), showed that OCS use results in a higher prevalence of comorbidities, including type II diabetes, hypertension and osteoporosis.[12] . It has been shown that *four or more* courses in a year is associated with significantly greater odds of a person developing osteoporosis, hypertension, obesity, type 2 diabetes, gastrointestinal ulcers/bleeds, fractures, and cataracts[13]. In fact, one study has shown that cumulative exposures, equivalent to just four courses of oral steroids over a lifetime, are associated with adverse outcomes.[14] Lehanne's life has been devastated by her severe asthma. *"Being on high doses of corticosteroids for such a long time has led to all sorts of health problems from their side effects including bone damage. I've had a hip replacement and surgery on my neck because my bones have weakened and I also live in constant pain from*

[10] Broadbent C, Pfeffer P, Steed L, Walker S, 'Patient-reported side effects of oral corticosteroids', (2018) European Respiratory Journal 2018 52: PA3144
[11] NHS England, Specialised Respiratory Services (adult) – Severe Asthma, Service Specification: 170002/S. Accessed at: https://www.england.nhs.uk/wp-content/uploads/2017/04/specialised-respiratory-services-adult-severe-asthma.pdf, July 2019.
[12] Sweeney J, Patterson CC, Menzies-Gow A, Niven RM et al. 'Comorbidity in severe asthma requiring systemic corticosteroid therapy: cross-sectional data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry'. Thorax 2016; 71:339-346 https://thorax.bmj.com/content/71/4/339
[13] https://www.ncbi.nlm.nih.gov/pubmed/28456623
[14] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6121746/

problems with my lower back. I am on regular nebulisers and cannot leave the house without my portable nebuliser. Daily, I take home infusions of Bricanyl and every five weeks I'm admitted to the Royal Brompton hospital for ten days treatment of intravenous infusion of aminophylline, hydrocortisone and physiotherapy."[15] Sadly, Lehanne, like many people with severe asthma, did not qualify for the biologics available at the time. She reflected:, *"life is an endless stream of good periods interspersed with episodes of deterioration which end with me being admitted to hospital. I spent last Christmas in hospital being intubated because I couldn't breathe. My husband is very understanding and does his best to help, but it's stressful and difficult for both of us. I'm desperate for new treatments as are so many of us who live with severe asthma. I really hope the new drugs becoming available will make a difference to our lives."* [16]

Biologic treatment

The introduction of biologics to treat asthma has proved to be life-transforming for people with severe asthma who are eligible for them. For example, Jane, who was diagnosed with severe eosinophilic asthma and started taking mepolizumab (another biologic treatment for severe asthma) said, *"Two weeks after my first injection I could climb hills in the Peak District. After just three injections, instead of contemplating taking early retirement from the midwifery job I love, I'm actually thinking about increasing the number of hours I do. This treatment has really transformed my life."*

Jenny was diagnosed with severe asthma and treated with a biologic after suffering from a sudden severe asthma attack whilst on holiday and ended up in hospital for 10 days. *"Since having monthly Xolair injections to reduce my allergic response, at least I'm able to go outside in summer now."*[17]

Our forthcoming qualitative report also highlighted the impact biologic treatment can have[18]. For example:

[15] Asthma UK, 'Press release: New generation asthma drug gets approval for NHS use', accessed at: https://www.asthma.org.uk/about/media/news/new-generation-asthma-drug-gets-approval-for-nhs-use/, (2017)
[16] Ibid
[17] Asthma UK, 'How I cope with severe asthma', accessed at: https://www.asthma.org.uk/advice/severe-asthma/your-stories-severe-asthma/how-i-cope-with-severe-asthma/
[18] Lottie Renwick, Asthma UK, 'Falling into isolation: Lived experience of people with severe asthma' (2020) Not yet published

	"What [the biologic] has also done is give me a sense of confidence…It has just provided that extra dimension of freedom, a psychological freedom, really. That's an invaluable thing. It's a really basic thing, not being sick all the time". (Participant 3) *"Well, I actually have a life now, because before I was on a mobility scooter. I was unable to do anything. I wasn't able to leave the house without the scooter. I just had no life. So, yes, it's come back now".* (Participant 5) In effect, except for biologic treatment, therapeutic options are limited for patients with severe asthma whose symptoms cannot be controlled with inhaled steroids and they often must rely on toxic oral steroids.
8. Is there an unmet need for patients with this condition?	The introduction of biologics for treating the condition has truly transformed the lives of many with severe asthma, but thousands may not be eligible for current treatments and even those that are eligible, may not respond to them. Therefore, we urgently need more biologic treatment options for those who have not responded to the biologics they are currently eligible for, as well as those not eligible for any biologic treatment at all. Our report, 'Living in Limbo', highlighted that only around 60,000 people with severe asthma are eligible for existing biologic treatments. This means around 140,000 people with severe asthma are not yet eligible for any biologic treatment. Furthermore, our report found that 4/5 of those eligible currently are not receiving biologic treatment. [19] There is therefore a large unmet need for effective treatments for people with severe asthma. Although existing biologics can reduce asthma attacks by >50%, their potential is limited in that they are only made available to specific sub-populations and they don't work for everyone.[20][21] Mepolizumab, for example, is currently only

[19] Asthma UK, 'Living in Limbo: the unmet need in difficult and severe asthma', Accessed at: https://www.asthma.org.uk/support-us/campaigns/publications/hidden-harm/living-in-limbo/
[20] Fasenra, 'considering fasenra', accessed at: https://www.fasenra.com/eosinophilic-asthma-treatment.html, accessed on 16/07/2019
[21] American Academy of allergy asthma and immunology, 'Mepolizumab: sustained safety and efficacy in severe eosinophilic asthma', accessed at:https://www.aaaai.org/global/latest-research-summaries/Current-JACI-Research/mepolizumab, (2018)

	available to patients who have had a blood eosinophil count of 300 cells/microlitre or more in the previous 12 months and have had 4 or more asthma exacerbations needing OCS in the previous 12 months, or who have had continuous OCS in the last six months.[22] Widening the population eligible for mepolizumab to the same criteria as other biologics such as reslizumab, will increase the chances of someone finding a biologic that works for them. Furthermore, expanding the criteria to those who are not eligible for any biologic could offer a lifeline to people who have no other choice but to take toxic oral steroids. There is also an unmet need for children with severe asthma. Currently, mepolizumab, reslizumab and benralizumab are all only recommended for adults (18 and over). The proposal to expand mepolizumab to include children aged 6 and over will therefore address a great unmet need in children with severe asthma. Tragically, we still see around 20 child deaths and thousands of hospital admissions in the UK every year from asthma. We also know that the UK has the highest rate of deaths from asthma for young people aged 10-24[23].
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Biologic treatment has transformed the lives of many with severe asthma. They offer people with severe asthma the opportunity to control their symptoms and live a life unhindered by their condition. As well as the reduction in symptoms, asthma attacks and hospital admissions, people with severe asthma are given a better quality of life with biologic treatment. As highlighted in the quotes above, they can do more, work, socialise and exercise, which they may not have been able to do before. This can also greatly alleviate pressure on family

[22] NICE, 'Mepolizumab for treating severe refractory eosinophilic asthma', accessed at: https://www.nice.org.uk/guidance/TA431/chapter/1-Recommendations
[23] https://www.nuffieldtrust.org.uk/news-item/uk-young-people-let-down-on-long-term-illness-new-international-report-finds

	members and carers.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Some people with severe asthma may have to travel great distances to their severe asthma centre for treatment, however with the introduction of home administration this is becoming less of a problem.
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.	N/A

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Our recent report, 'The Great Asthma Divide: Annual Asthma Survey 2019' has shown that those on lower incomes are more likely to have uncontrolled asthma and experience more asthma attacks[24]. Therefore, they may be more adversely impacted by severe asthma.
Other issues	
13. Are there any other issues that you would like the committee to consider?	
Key messages	
15. In up to 5 bullet points, please summarise the key messages of your submission: • Severe asthma is so much more than asthma attacks and hospital admissions. It can have devastating consequences on every aspect of people's lives. They may feel isolated, lonely and scared, left without hope or the right support.	

[24] Andrew Cumella, Asthma UK, The Great Asthma Divide: Annual Asthma Survey 2019, (2020) Accessed at: https://www.asthma.org.uk/58a0ecb9/globalassets/campaigns/publications/The-Great-Asthma-Divide.pdf

- There is a substantial unmet need for people with severe asthma in the treatment options available to them. They may have to rely largely on high doses of OCS to control their symptoms, which can have toxic side effects such as osteoporosis and diabetes.[25]
- The introduction of biologics for treating the condition has truly transformed the lives of many with severe asthma, but thousands may not be eligible for current treatments and even those that are eligible, may not respond to them.
- Widening the population eligible for mepolizumab to the same criteria as other biologics such as reslizumab, will increase the chances of someone finding a biologic that works for them.
- Expanding the criteria to those who are not eligible for any biologic could offer a lifeline to people who have no other choice but to take toxic oral steroids.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

[25] Asthma UK, https://www.asthma.org.uk/advice/inhalers-medicines-treatments/steroids/ (accessed 12/02/2019)

NICE National Institute for Health and Care Excellence

Clinical expert statement

Mepolizumab for treating severe eosinophilic asthma [ID3750]

Thank you for agreeing to give us your 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.

Information on completing this expert statement

- 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
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Ian Pavord**
2. Name of organisation	**University of Oxford and Oxford University Hospitals Foundation Trust**

3. Job title or position	**Professor of Respiratory Medicine and Honorary Consultant Physician**
4. Are you (please tick all that apply):	**x**☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x**☐ a specialist in the treatment of people with this condition? **x**☐ a specialist in the clinical evidence base for this condition 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)	**x**☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't 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

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To reduce exacerbations of severe eosinophilic asthma and exposure to oral corticosteroids
8. 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.)	>30% reduction in exacerbations is generally regarded as a clinically important reduction although it depends on the baseline rate (i.e. lower % reductions would be important in patients with a high baseline rate). >50% reduction in oral corticosteroid dose
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Severe asthma is responsible for the bulk of the morbidity and mortality due to asthma and about 80% of healthcare-related costs
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Maximum dose inhaled corticosteroids and long acting beta-2 agonists. Most patients are also taking a large number of minimally effective treatments such as inhaled long acting anti-muscarinics, montelukast, theophylline and carbocysteine. Pre-biologics, 40% of patients with severe asthma required long-term oral corticosteroid treatment at a dose of 10-15 mg/day. This treatment is associated with well-known adverse effects.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	GINA severe asthma guidelines, updated in 2020 are the most widely used. There were also ATS/ERS severe asthma guidelines published in 2014 and the BTS/SIGN guidelines have some severe asthma recommendations.
• 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.)	Yes, there are well defined algorithms. The response to the anti-IL-5 biologics is closely related to the peripheral blood eosinophil count so this is a targeted treatment (the only biologic for non-malignant disease used in this way). As a result, treatment is given to the patients most likely to have a good response. The current NICE criteria for use of anti-IL-5 biologics (4 or more exacerbations and a blood eosinophil count >300 cells/mcl) are widely accepted by the clinical community because the rationing is rationale (being based on the blood eosinophil count and prior exacerbation frequency). There are some inequities as mepolizumab can only be used with 4 or more exacerbations in the last year whereas beralizumab and reslizumab can be used with 3 or more provided the eosinophil count is >400 cells/mcl. This difference makes no sense as the drugs have very similar efficacy and the clinical community would like treatment criteria to be standardised.
• What impact would the technology have on the current pathway of care?	The biological agents have already had a massive impact in severe asthma, reducing the new use of regular oral corticosteroids in severe asthma centres to nothing in just 5 years. 80% of treated patients have a positive response to treatment (>50% reduction in exacerbations and/or oral corticosteroid dose) and 40% are super-responders (no exacerbations and complete withdrawal from oral corticosteroids). Many also see an improvement in symptoms and lung function. In the 30% of patients with severe eosinophilic asthma and a baseline blood eosinophil count >500 cells/mcl the symptom and lung function

	response to anti-IL-5 is huge and would be difficult to achieve with any other intervention. There is a strong argument to allow prescribing of biologics with a lower exacerbation frequency in this subgroup. I'm surprised that the companies are not asking ft this. Clinicians in severe asthma certainly are as anti-IL-5 has a massive positive impact in this sub-group.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes. In the UK biological treatment for severe asthma is prescribed and supervised by severe asthma centres, most of which serve >2 million population and operate a hub and spoke type arrangement with surrounding general hospitals. There is a good deal of shared care and the system works very well. There is evidence that biologics are used more economically and effectively in the UK compared to neighbouring countries
• How does healthcare resource use differ between the technology and current care?	My understanding is that GSK are requesting similar use criteria to those available for reslizumab and benralizumab.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	In existing severe asthma centres (tertiary care).
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None. Infa-structure is already in place, The requested change in prescribing criteria will have minimal impact on the total use of biologics but might mean a higher proportion of patients are eligible for mepolizumab, the anti-IL-5 with the longest post-marketing experience and more robust efficacy and safety data
12. Do you expect the	See above.

technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	Yes, very likely by reducing asthma deaths and deaths due to oral corticosteroid associated morbidity. This has not been firmly established.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. There are large improvements in the St George's Respiratory Questionaire (SGRQ) of 7 points (MCID 4), particularly in the 30% with a baseline blood eosinophil count >500 cells/mcl (12 points). This efficacy would be impossible to achieve with other treatments. For example, long-acting antimuscarinics (a NICE approved intervention) improve SGRQ by <2 points.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes. The blood eosinophil count is a terrific predictive biomarker (see above).
The use of the technology	
14. Will the technology be easier or more difficult to use	Easier than reslizumab, which requires an intravenous injection every month. The infrastructure for administering and supervising biologic treatment in asthma is well established and works well. Most

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.)	patients now self-inject at home and do this very well.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	About 20% fail to achieve treatment goals and stop treatment after a year. There is a small amount of between biologic swapping of treatment before 12 months but this is not evidence based and management algorithms are not well established.
16. 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	This is a game-changing treatment in the right patient (‘I have my life back’). It is frustrating that the PROs (with the exception of the SGRQ, see above) do not really pick this benefit up. The benefits of reduced oral corticosteroids are huge but have been difficult to quantify and monetarise.

quality-adjusted life year (QALY) calculation?	
17. 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?	Highly innovative and remarkably successful. Has largely replaced the use of regular oral corticosteroids in severe asthma. Some patients also notice an improvement in upper airway symptoms (I.e. those due to nasal polyps, a common comorbidity).
• Is the technology a 'step-change' in the management of the condition?	Yes. See above for details. Described as the most important advance in the last 50 years of asthma treatment in the recent 2018 Lancet Commission on Asthma.
• Does the use of the technology address any particular unmet need of the patient population?	Exacerbations and need for regular and rescue oral corticosteroids. Symptoms (upper and lower airway) and lung function also improve very significantly in some (see above).
18. How do any side effects or adverse effects of the technology affect the	Injection site reactions only. Biologics targeting eosinophilic airway inflammation have proved to be remarkably safe.

management of the condition and the patient's quality of life?	
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. Very well defined patient population and well validated predictive biomarker.
• 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?	Exacerbations; requirement for oral corticosteroids
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
• Are there any adverse effects that were not apparent in clinical trials but have come to light	There may be a small increased risk of shingles and some clinicians offer prophylactic vaccination. Not well established.

subsequently?	
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA431, TA479 and TA565?	Dupilumab is currently being assessed by NICE. It is a biological agent targeting a different arm of type-2 immune response (IL-13 and IL-4 by blocking the IL-4 receptor alpha). The effects are very similar, with a similar relationship between efficacy and the blood eosinophil count. Dupilumab seems to be more effective for upper airway problems. Exhaled nitric oxide is also a good predictive biomarker of response to dupilumab but not anti-IL-5.
22. How do data on real-world experience compare with the trial data?	Reality-A, a large multicentre international real world study has shown a 69% reduction in exacerbations and a 50% reduction in oral corticosteroid dose with mepolizumab
Equality	
23a. Are there any potential equality issues that should be taken into account when	No

considering this treatment?	
23b. Consider whether these issues are different from issues with current care and why.	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your statement.

- Highly effective and safe treatment
- We have a clinically accessible and well validated predictive biomarker (blood eosinophils).
- Treatment is administered responsibly and efficiently in the UK by a network of severe asthma centres
- The impact on severe asthma care has been huge. We no longer use regular oral corticosteroids to treat new cases of severe asthma
- The clinical community is pleased that the rationing suggested by NICE is entirely rational. However, they would like access to the different anti-IL-5s to be equitable.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

NICE National Institute for Health and Care Excellence

For more information about how we process your personal data please see our privacy notice.

.....

NICE National Institute for Health and Care Excellence

Patient expert statement

Mepolizumab for treating severe eosinophilic asthma [ID3750]

Thank you for agreeing to give us your 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.

Information on completing this expert statement

- 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
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Peter McQuitty**
2. Are you (please tick all that apply):	☐ a patient with the condition

3. Name of your nominating organisation	Asthma UK, British Lung Foundation Partnership
4. Did your nominating organisation submit a submission?	☐ FTA
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)	☐ FTA

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.)	☐
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	I have been severely asthmatic since the age of two, over 60 years. Scientific understanding of the causes of asthma and effective treatments for it were limited until relatively recently and I only received an accurate diagnosis about five years ago. On the basis of that diagnosis I was prescribed Mepolizamub. Prior to that I was subject to very regular and debilitating attacks. This led to regular time off school and work, and frequent hospitalisations. Exercise and sport were very difficult. Over the years very few prescribed medications worked and I was prescribed ever more regular doses of antibiotics and oral corticosteroids. Over time the oral steroids led to heavy weight gain and resulting blood pressure problems. As a result of both physical and psychological pressures, my quality of life was extremely poor. The stress caused to carers and family members from the severity and uncertainty of this condition is immense. The asthmatic and family members all felt both helpless and hopeless.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Diagnosis of asthma was for many years not well informed scientifically and resulting treatment was very hit and miss, often down to GP prejudice rather than science. I vividly remember a GP in my youth telling my mother that my asthma was a result of her divorce. A more scientifically rigorous approach to diagnosis combined with the new generation of biologic treatments have the potential to transform the health and personal and working lives of many people particularly by freeing them from the very negative consequences of corticosteroids. The new treatments should mean that children and young people should not in future have to live with the levels of disability that impacted my generation. There should be no reason why severe asthmatics should not be able to live full lives, contributing fully to the economy.
10. Is there an unmet need for patients with this condition?	In my experience of the asthma community there is huge need for new, safe biologic treatments. There is also a huge need for better education of GPs about the causes and new treatments for asthma.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Following successful participation in a clinical trial for Mepolizamub the drug was prescribed for me. It has transformed my life. In the five years or so that I have been taking Mepo I have not been hospitalised and I have not required any oral corticosteroids. I have been able to exercise again, I have lost over two stone in weight and my blood pressure is now normal again. At my age, and with my history of asthma, I had not expected ever to be able to live normally. I am extremely grateful to the clinicians who accurately assessed my condition and prescribed this for me and the researchers who developed the drug.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	In my experience, there have been no disadvantages. I have had no adverse side effects from the drug and the self-injection regime is extremely convenient.

Patient population	
13. 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.	See above.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	A more personalised approach to medicine – more scientifically based diagnosis and more accurate prescription - should mean greater equality of treatment. There are obviously many questions around wider health inequalities but these are political as much as medical issues.
Other issues	
15. Are there any other issues that you would like the committee to consider?	

Key messages
16. In up to 5 bullet points, please summarise the key messages of your statement: • Mepolizamub has transformed every aspect of my life. • More personalised medicine - scientifically-based diagnosis and relevant treatment - can deliver strong results. • Desperate need for better GP training re the causes of asthma and new treatments for it. • GPs in particular need to understand the damage that oral corticosteroids can cause. • •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

NICE National Institute for Health and Care Excellence

Patient expert statement

Mepolizumab for treating severe eosinophilic asthma [ID3750]

Thank you for agreeing to give us your 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.

Information on completing this expert statement

- 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
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Lottie Renwick**
2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition? ☒ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Asthma UK
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
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 didn't submit one, I don't 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

Mepolizumab for treating severe eosinophilic asthma (review of technology appraisal guidance TA431) [ID3750]

Produced by	**Peninsula Technology Assessment Group (PenTAG)** University of Exeter Medical School South Cloisters St Luke's Campus Heavitree Road Exeter EX1 2LU
Authors	**Brian O'Toole**[1] **Elham Nikram**[1] **Sophie Robinson**[1] **David A Scott**[1,2] **G.J. Melendez-Torres**[1] [1] Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School, Exeter
Correspondence to	G.J. Melendez-Torres 3.09 South Cloisters, St Luke's Campus, Heavitree Road, Exeter, EX1 2LU; g.j.melendez-torres@exeter.ac.uk
Date completed	27/07/2020
Source of funding	This report was commissioned by the NIHR Systematic Reviews Programme as project number 13/14/86.
Declared competing interests of the authors	None
Acknowledgments	The authors acknowledge: the project management and coordination, and draft review and comments provided by Louise Crathorne (PenTAG), clinical advice provided by David Halpin (Royal Devon and Exeter NHS Foundation Trust), and the administrative support provided by Sue Whiffin (PenTAG) and Jenny Lowe (PenTAG).
Rider on responsibility for document	The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows	O'Toole B, Nikram E, Robinson S, Scott DA, Melendez-Torres G.J. Mepolizumab for treating severe eosinophilic asthma (review of technology appraisal guidance TA431) [ID3750]. Peninsula Technology Assessment Group (PenTAG), 2020.
Copyright	

Author Contributions:	Brian O'Toole conducted the critique of the cost comparison. Elham Nikram, G.J. Melendez-Torres and David A Scott conducted the critique of the indirect treatment comparison. Sophie Robinson conducted the critique of the company searches. All authors contributed to the writing and formatting of the report. G.J. Melendez-Torres is guarantor of the report.

Template Date	July 2017

Table of Contents

List of Tables

List of Figures

Abbreviations

ACQ	Asthma Control Questionnaire
AE	adverse event
BNF	British National Formulary
BRL	Benralizumab
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CS	company submission
ED	emergency department
ERG	Evidence Review Group
FEV_1	forced expiratory volume in one second
FTA	fast track appraisal
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
ICS	inhaled corticosteroids
IL	Interleukin
ITC	indirect treatment comparison
ITT	intention to treat
IV	Intravenous
LABA	long acting beta-agonist
MAIC	matching adjusted indirect comparison
MPL	Mepolizumab
mths	Months
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NR	not reported
OCS	oral corticosteroids
OWSA	one-way sensitivity analysis
PAS	patient access scheme
PBO	Placebo
PSA	probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit

Q*X*W	every *X* weeks (where X is number of weeks)
QALY	quality adjusted life year
RCT	randomised controlled trial
RR	risk ratio
RSL	Reslizumab
SC	Subcutaneous
SD	standard deviation
SLR	systematic literature review
SPC	summary of product characteristics
TA	technology appraisal
Tx	Treatment
UK	United Kingdom
vs	Versus
WTP	willingness to pay
yrs	Years

1. SUMMARY OF THE EVIDENCE REVIEW GROUP'S VIEW OF THE COMPANY'S FTA CASE

1.1. The technology is pharmacologically similar to the comparator

In TA565, the committee determined that biological treatments for people with severe eosinophilic asthma that is inadequately controlled, despite taking high-dose inhaled corticosteroids and long-acting beta-agonists, aim to both reduce the number and severity of exacerbations and reduce or avoid the use of oral corticosteroids. The committee concluded that benralizumab, although having a different mechanism of action to mepolizumab and reslizumab, also acts by reducing eosinophils and therefore was an appropriate comparator. The ERG considered there to be no reason that this would be any different for this appraisal.

1.2. The specified population is appropriate

The population specified in the National Institute for Health and Care Excellence (NICE) final scope was people aged six years and older with severe refractory eosinophilic asthma. Mepolizumab is currently recommended for adults with severe refractory eosinophilic asthma with a blood eosinophil count of ≥300 cells/μl and who have had ≥4 exacerbations in the previous 12 months. Given this, the CS decision problem focuses on a narrower population: adults with severe refractory eosinophilic asthma with a blood eosinophil count of ≥400 cells/μl and who have had ≥3 exacerbations in the previous 12 months as this population can currently access reslizumab and benralizumab, but not mepolizumab. The rationale for this focus was to align the recommendation for mepolizumab with that of benralizumab i.e. baseline eosinophil count of ≥300 cells/μl and who have had ≥4 exacerbations in the previous 12 months or baseline eosinophil count of ≥400 cells/μl and who have had ≥3 exacerbations in the previous 12 months. Given prior scrutiny of the broader population by NICE and the existing recommendations (TA431, TA479, and TA565), the ERG did not consider the focus on this subgroup to be an issue. Refer to Section 2.1 for additional discussion on this point.

1.3. The selected comparators are appropriate

Both benralizumab and reslizumab were provided as comparators in this submission. However, the company states that reslizumab is the primary comparator. The company acknowledged that as the aim of this appraisal was to align the recommendation for mepolizumab with that of benralizumab in TA565[1] (Table 1), the main comparator should be benralizumab. Noting the lack of data presented for the subgroup in TA565, the company considered that additional

effectiveness data should be presented together with a cost comparison with reslizumab. While it acknowledged the company's rationale, the ERG noted that the primary comparator used in the analysis should be the treatment which will most likely be displaced in clinical practice, which is arguably benralizumab. In TA565 mepolizumab was judged to have similar overall health benefits to benralizumab. The company presented results versus both comparators in the CS. Given the focus of the submission was the subgroup of patients with baseline blood eosinophil count in the previous 12 months of ≥400 cells/μl with ≥3 severe exacerbations needing corticosteroids in the previous 12 months, the existing NICE recommendations in this regard, and no substantial changes to the pathway since TA565, the ERG did not consider this to be a substantial issue. Refer to Section 2.3 for additional discussion on this point.

1.4. The specified outcomes are appropriate

Study outcomes reported for the included studies (comparisons vs placebo) were appropriate to the decision problem presented, and aligned with prior technology appraisals (Section 2.4), despite the absence of some outcomes specified in the NICE final scope; for example, oral corticosteroid (OCS) use. However, clinical advice to the ERG suggested that a reduction in exacerbations may also imply a reduction in steroid use so the ERG does not consider this an issue, rather a point of discrepancy versus the prior technology appraisals (TAs). The ERG considered that the outcomes included were appropriate to the decision problem presented.

1.5. Evidence provided in support of similarity between intervention and comparators

While the ERG noted limitations in the systematic review methods (Section 3.1) and reporting relevant to the subgroup in focus for this appraisal, it considered it unlikely that key evidence had been missed based on its scrutiny of other published systematic reviews in the population. Despite the lack of clarity in reporting (Section 2.1), the ERG did not regard that additional uncertainty was generated.

There were no direct head to head data comparing mepolizumab to reslizumab or benralizumab. As such the assumption of comparable efficacy which underpinned the cost comparison was dependent on an ITC by Busse et al. 2019.[2] However, the range and extent of clinical evidence submitted to inform the ITC, included nine randomised controlled trials (RCTs). Despite between study variation in respect of length of follow-up, dosing regimens and administration, asthma severity, baseline blood eosinophil counts, and prior exacerbations, most pairwise meta-analyses had low heterogeneity. Studies were of low risk of bias; however, the

ERG noted that, for mepolizumab and benralizumab, data were from a subgroup of the ITT population and therefore standard statistical significance thresholds may not apply.

While the company presented some data for the specific subgroup of interest (baseline eosinophil count ≥400 cells/μl and ≥3 exacerbations), during clarification (clarification question A9), these data were inconsistently available for the comparators, in part due to redaction in previous appraisals. Data analyses were, however, presented for the broader subgroup of participants with baseline eosinophil count ≥400 cells/μl. Based on inclusion criteria these participants all had at least one (reslizumab) or two (mepolizumab and benralizumab) severe exacerbations in the previous 12 months, so although the subgroup was not precisely aligned to the recommendation extension, the ERG regarded that in principle it was closer than not. While it was not possible to comprehensively assess this in respect of the modification of treatment effect, the ERG considered that it would not substantively alter the conclusion regarding similar or greater effectiveness. Overall, the ERG considered this to be a reasonable approach.

Subgroup data for participants with baseline eosinophils ≥400 cells/μl were available for RCTs to inform at least one comparison of mepolizumab against another drug for all outcomes for which meta-analysis was attempted. Key outcomes assessed included exacerbation, exacerbations requiring ED visits/hospitalisation, ACQ scores and FEV_1. Despite some limitations (Section 3.2.3), the ERG regarded that both the methods used for the ITC and the interpretation of the results were broadly appropriate. The ERG further regarded that mepolizumab generally provided similar, if not better, effectiveness as compared to benralizumab and reslizumab within the focal subgroup.

1.6. Cost comparison approach was applicable

The company submitted a simple cost comparison which compared treatments based on medicine acquisition costs, administration and monitoring costs only. The ERG considered that this is likely to be appropriate on the basis that comparable efficacy between treatments has been demonstrated (see Section 4.1.1). Drug acquisition costs were considered to be the key driver of mepolizumab incremental savings within the company's analysis (see Section 4.1.5.1). Monitoring and administration costs were included on the basis that these costs will differ between treatments according to route of administration and dose frequency; however, these did not appear pivotal to the company's case (see Table 11 in Section 4.1.5.1). Overall, the company's decision to conduct a FTA is considered reasonable based on the clinical evidence submitted.

1.7. Strength of the case for undertaking an FTA

Evidence indicates that there is a low risk that mepolizumab is less effective than other available anti-IL5 treatments for severe eosinophilic asthma as recommended by NICE. The strength of the company's case for undertaking an FTA appeared to depend on the cost comparison modelling, and in the appropriateness of comparator choice.

2. CRITIQUE OF THE DECISION PROBLEM IN THE COMPANY'S SUBMISSION

The decision problem assesses the anti-interleukin (IL) 5 treatment mepolizumab (marketing authorization holder: GlaxoSmithKline) for the treatment of adults with severe eosinophilic asthma. The European Medicines Agency granted a marketing authorization throughout the EU on 2 December 2015.[3] The EU marketing authorization was extended in August 2018 to include paediatric patients (aged six to 11 years),[4] and again in August 2019 to include an EU marketing authorization for self-administration using pre-filled pen or pre-filled syringe in people aged 12 years-plus.[5]

The Evidence Review Group (ERG) considered the company's description of the underlying health problem in the company's submission (CS) to be appropriate and relevant to the decision problem set out in the final NICE scope. The ERG's considerations in respect of population, intervention, comparators, and outcomes assessed is provided below.

2.1. Population

The population specified in the NICE final scope was people aged six years and older with severe refractory eosinophilic asthma. Eosinophilic asthma is a phenotype of asthma characterized by the higher than normal presence of eosinophils in the lung and sputum. It has been shown that the numbers of eosinophils in the blood and bronchial fluid correlate with asthma severity. The CS decision problem focused on a narrower population: adults with severe refractory eosinophilic asthma with a **blood eosinophil count of ≥400 cells/µl and who have had ≥3 exacerbations in the previous 12 months**, as this population can currently access reslizumab and benralizumab, but not mepolizumab. The company's rationale for this focus was that the purpose of this appraisal was to update the existing recommendation for mepolizumab (technology appraisal TA431[6]) to align with the recommendation for benralizumab resulting from TA565.[1] Given prior scrutiny by NICE of mepolizumab, reslizumab, and benralizumab for the adult population in TA431, TA479,[7] TA565, respectively – in particular recommendations resulting from TA565 – and clinical advice to the ERG in respect of the CS, the ERG did not, in principle, consider the proposed focus on the subgroup with blood eosinophil count of ≥400 cells/µl and who have had ≥3 exacerbations in the previous 12 months to be an issue.

No comparative data were available for the subgroup with a blood eosinophil count of ≥400 cells/µl and ≥3 exacerbations in the previous 12 months. However, key comparative efficacy

data in the population with a **blood eosinophil count of ≥400 cells/µl** (mepolizumab vs reslizumab, mepolizumab vs benralizumab, and reslizumab vs benralizumab), were provided from a published ITC (Busse et al., 2019[2]) including nine placebo-controlled RCTs. Based on inclusion criteria, for the RCTs participants all had at least one (reslizumab) or two (mepolizumab and benralizumab) severe exacerbations in the previous 12 months. Acknowledging that matching of exacerbation history is of particular importance given effect modification of treatment efficacy by exacerbation history, the ERG regarded that while the broader subgroup was not exactly aligned to the recommendation extension, in principle it was closer than not. While it was not possible to comprehensively assess this in respect of the modification of treatment effect, the ERG considered that it would not substantively alter the conclusion regarding similar or greater effectiveness. In addition, the company also provided data from the published ITC for a more restricted population with a **blood eosinophil count of ≥400 cells/µl and who have had ≥4 exacerbations in the previous 12 months** (mepolizumab vs reslizumab), the results of which were broadly aligned with the broader population. Overall, the ERG considered it to be a reasonable approach, particularly in context of TA565,[1] for which equivalent efficacy for benralizumab compared with reslizumab was based on an assumption.

2.2. Intervention

Mepolizumab has a marketing authorization in the UK as an add-on treatment for severe refractory eosinophilic asthma in adults, adolescents, and children aged six-years plus.[3] The recommended dose of mepolizumab is 100 mg administered subcutaneously once every four weeks. This meant that the 75 mg intravenous (IV) dose of mepolizumab was excluded despite it being bioequivalent to the 100 mg SC dose. During clarification, the company provided a pairwise analysis of mepolizumab against control for the outcome of clinically significant exacerbations, newly including a trial with the 75 mg dose; inclusion did not, however, impact the results and, as such, the ERG did not consider this to be an issue. The company was asked during clarification (clarification question C1) regarding its intention in respect of the broader license but in response clarified that the CS was focused on the adult population aligned with the comparators and current NICE recommendations. All authorised formulations of mepolizumab – solution for injection, prefilled syringe, and prefilled pen – were considered in the cost comparison presented in the CS.

2.3. Comparators

The NICE final scope included as potential comparators:

- reslizumab and benralizumab for people with severe asthma for whom biologics are indicated and recommended according to NICE guidance; and,
- optimized standard therapy without biologics for people with severe asthma for whom currently available biologics are not indicated and suitable.

The company's decision problem does not address the NICE final scope for the comparator interventions in full, and focuses only on reslizumab and benralizumab. Based on the existing NICE recommendations for the specified anti-IL5 treatments in the population (Table 1). The company acknowledged that as the aim of this appraisal was to align the recommendation for mepolizumab with that of benralizumab (Table 1), the main comparator should be benralizumab. However, given the lack of data presented for the subgroup in TA565, the company considered that additional effectiveness data should be presented together with a cost comparison with reslizumab. The company also noted that in TA565 (benralizumab) (i) the committee and the ERG concluded that mepolizumab and benralizumab had similar clinical effectiveness and were cost-effective for the eligible populations based on a mixed adjusted indirect comparison (MAIC); and (ii) the assumption of equivalent efficacy for benralizumab and reslizumab in the CS and the demonstration of cost-effectiveness of benralizumab compared with reslizumab in the ERG's analysis. Both reslizumab and benralizumab were therefore considered as comparators in the submission and data presented for mepolizumab compared with both in the submission. Given the focus of the submission was on the subgroup of patients with blood eosinophil count in the previous 12 months of ≥400 cells/μl with ≥3 severe exacerbations needing corticosteroids in the previous 12 months, and the existing NICE recommendations in this regard, the ERG did not consider this to be a substantive issue.

Table 1: Current recommendations: MPL (TA431), RSL (TA479), and BRL (TA565)

	TA431 MPL 2016	TA479 RSL 2017	TA565 BRL 2018
Population	Add-on to optimised standard therapy as an option for treating severe refractory eosinophilic asthma in adults, if:	Add-on therapy as an option for treating severe eosinophilic asthma that is inadequately controlled in adults despite maintenance therapy with high-dose ICS plus another drug, if:	Add-on therapy as an option for treating severe eosinophilic asthma that is inadequately controlled in adults despite maintenance therapy with high-dose ICS and LABAs plus another drug, if:

	TA431 MPL 2016	TA479 RSL 2017	TA565 BRL 2018	
Optimised standard treatment plan	Agreed to and followed optimised standard treatment plan **and**	NA	Agreed to and followed optimised standard treatment plan **and**	
Blood eosinophil count in previous 12 months	≥300 cells/μL **and**	≥400 cells/μL **and**	≥300 cells/μL **and**	≥400 cells/μL **and**
Severe asthma exacerbations	≥4 needing corticosteroids in the previous 12 months **or**	≥3 needing corticosteroids in the previous 12 months **and**	≥4 needing corticosteroids in the previous 12 months **or**	≥3 needing corticosteroids in the previous 12 months **and**
Treatment	Continuous oral corticosteroids (OCS) of at least the equivalent of prednisolone 5 mg per day over the previous 6 months **and**	NA	Continuous OCS of at least the equivalent of prednisolone 5 mg per day over the previous 6 months **and**	NA
Price	As per agreed PAS	As agreed in the PAS	As per commercial arrangement	

Abbreviations: BRL, benralizumab; ICS, inhaled corticosteroids; LABAs, long-acting beta agonists; MPL, mepolizumab; NA, not applicable; PAS, patient access scheme; RSL, reslizumab

2.4. Outcomes

The outcomes considered in the CS included exacerbation requiring treatment with OCS; exacerbation requiring an ED visit/hospitalization; ACQ score; and lung function (change from baseline pre-bronchodilator FEV_1). The ERG noted that the company's positioning of Busse et al. (2019)[2] as the key comparative evidence was likely the primary driver for the selection of these outcomes. The ERG noted that the CS did not explicitly present evidence for the outcomes use of OCS, patient and clinical evaluation of response, mortality, time to discontinuation, adverse effects (AEs), and health-related quality of life (HRQL) for mepolizumab relative to benralizumab or reslizumab. While use of OCS was among the outcomes missing, clinical advice to the ERG suggested that a reduction in exacerbations may also imply a reduction in OCS use so the ERG did not consider this to be an issue. In addition, the committee decisions for TA479 and TA565 concluded that should the potential benefits of OCS sparing be included in an economic analysis, this would likely lower the ICER due to potential QALY gains through improved health-related quality of life. Overall, and in context of the previous TAs within this population, the ERG considered that the outcomes included were appropriate to the decision problem.

3. CLINICAL EFFECTIVENESS

The submission comprised Document A. FTA summary for committee, Document B (FTA – cost-comparison) and Document B (Appendices). In this ERG report, CS refers to Document B and related appendices. The ERG report also refers to relevant additional material submitted by the company in response to the clarification request from NICE.

3.1. Summary and critique of the company's systematic review

The company's approach to the identification of studies relied predominantly on existing reviews: TA431 and Busse et al. (2019)[2] and an update search which was, in part, based on TA431. During clarification the company also noted that, despite the search dates 2015 to current, the update had been used to confirm that no direct comparative evidence or other relevant placebo controlled RCTs had published since the publication of the Busse et al. ITC.

As the original searches were critiqued in TA431, the ERG did not comment further in this report. The company in part updated the searches conducted in TA431 in 2015; however, these searches had some problematic aspects: in most cases no subject heading/supplementary concept searches had been carried out; only one database was searched (Medline via PubMed); the RCT filter used was not a validated published filter such as that from the Cochrane Handbook.[8] Searches were therefore considered incomplete and likely to have missed relevant information.

The PICOS inclusion and exclusion criteria specified in the CS (Appendix E, Table 66), were aligned with the NICE final scope and appropriate adjustment had been made to reflect the different comparators in scope for this appraisal (refer to Appendix A). No studies were identified in the update searches. Based on information received from the company during clarification, the ERG assumed that this was, in part, due to the partitioning of studies already included in Busse et al. (2019).[2] Despite this, however, no attempt was made by the company to reconcile these differences in respect of the PRISMA flow diagram, and – accounting also for identified discrepancies, in part, resolved during clarification – the ERG was unable to establish the final number of included studies meeting eligibility criteria for this appraisal.

The company positioned an ITC conducted by Busse et al. (2019) as the key comparative evidence for the appraisal.[2] The primary data source for the ITC was the Cochrane review of anti-IL5 pathway-directed therapies developed in severe asthma. The search strategy used for conducting the systematic review, which was undertaken to identify randomized placebo-

controlled trials comparing mepolizumab, reslizumab, or benralizumab in adults and adolescents with asthma, is detailed within the Cochrane report (Cochrane searches carried out in March 2017). For the ITC, additional searches were carried out in January 2018 to identify any additional publications or relevant data sets (e.g., subgroup analyses) since March 2017. European Medicines Agency, US Food and Drug Administration, and National Institute for Health and Care Excellence documents, as well as ClinicalTrials.gov postings, were checked to identify any additional published subgroup analyses. In addition, any published meta-analyses for reslizumab and benralizumab using individual patient data potentially investigating subgroups were identified by searching PubMed.[2] The PICOS inclusion and exclusion criteria specified in the CS, were narrower than those reported in Appendix E of the CS. In particular, the focus on efficacy outcomes at the expense of other outcomes specified in the scope e.g. patient and clinician evaluation of response, reduction in OCS use, health-related quality of life, safety (including AEs, mortality, discontinuation). Despite this, overall and in context of the previous TAs within this population, the ERG considered that the outcomes included were broadly appropriate to the decision problem.

While the ERG did not consider any of the identified issues to be substantive, it did consider that the lack of clarity in reporting had added an unnecessary layer of complexity to the company's presentation of evidence in the CS. Moreover, the ERG considered that efforts to apply the ITC from Busse et al. (2019)[2] without appropriate elaboration, expansion or reporting in context of the decision problem in the CS had contributed to issues with the clarity of reporting. However, despite these deficiencies, the ERG did not regard that additional uncertainty was generated. In respect of the current recommendation, the ERG was satisfied that, despite limitations identified with the searches, scrutiny of other published systematic reviews and guidelines within the population suggested that no new evidence was available that would alter prior decision making.

3.2. Summary and critique of clinical effectiveness evidence submitted

The ERG noted that the clinical effectiveness evidence presented was broadly aligned with the evidence included in previous technology appraisals (TA431, TA479, and TA565). An evidence summary is provided in Appendix B (Table 19). During clarification (clarification question A6), the company noted that a total of five trials had been identified as ongoing as of January 2020.

Mepolizumab: Two of the RCTs presented in the CS compared mepolizumab with placebo in 355 participants with a blood eosinophil count of ≥400 cells/μl.[9,10] Studies were judged by the

company to have a low risk of bias. The ERG noted that the DREAM[11] and MENSA studies both included treatment arms evaluating 75 mg IV which is bioequivalent to mepolizumab100 mg SC. The company clarified that these 75 mg treatment arms from DREAM and MENSA were omitted from the ITC to ensure that the interventions evaluated reflected routine clinical practice. However, during clarification (clarification response A11, Table A11.2), the company provided a further set of meta-analyses including the 75 mg dose.

Benralizumab: Two of the RCTs presented in the CS compared benralizumab with placebo in 604 participants; these were reported in three publications, Bleecker 2016,[12] FitzGerald 2016[13] and FitzGerald 2018.[14] The ERG noted that this assessment was also aligned with the risk of bias assessment in the Cochrane review.[15]

Reslizumab: Four RCTs presented in the CS compared reslizumab against placebo and reported a subgroup of patients with a blood eosinophil count of ≥400 cells/μl; these were reported in four papers, Bjermer 2016[16] [Study 3081]; Castro 2015[17] and Brusselle 2017[18] [Study 3082 and 3083]; Corren 2016[19] [Study 3084]. In addition, in Castro 2015 participants were required to have a history of ≥1 exacerbation in the preceding 12 months. In addition, the Phase 2 trial, NCT00587288 (Castro 2011[20]), was not reported with the overview of trials but was used in the ITC (Section 3.2). Studies were judged by the company to have a low risk of bias. The ERG agreed but noted that risk of bias was unclear in respect of selection bias (random sequence generation and allocation concealment) and detection bias (blinding of outcome assessment).

The ERG noted that despite between study variation in respect of length of follow-up (from 15 to 52 weeks), standard of care therapy (severe or moderate-to-severe), eosinophil count at treatment initiation (baseline eosinophils ≥150 cells/μl to ≥300 cells/μl depending on time of measurement in the mepolizumab and benralizumab studies and baseline eosinophils ≥400 cells/μl), and number of exacerbations in the previous 12 months (from ≥1 to ≥2), most pairwise meta-analyses had low heterogeneity.

Studies were judged of low risk of bias; however, the ERG noted that, for mepolizumab and benralizumab, data were from a subgroup of the ITT population and therefore standard statistical significance thresholds may not apply.

No head-to-head trials were identified, thus the directly estimated relative effectiveness of these treatments is not known. The company presented the published ITC, published in Busse et al.

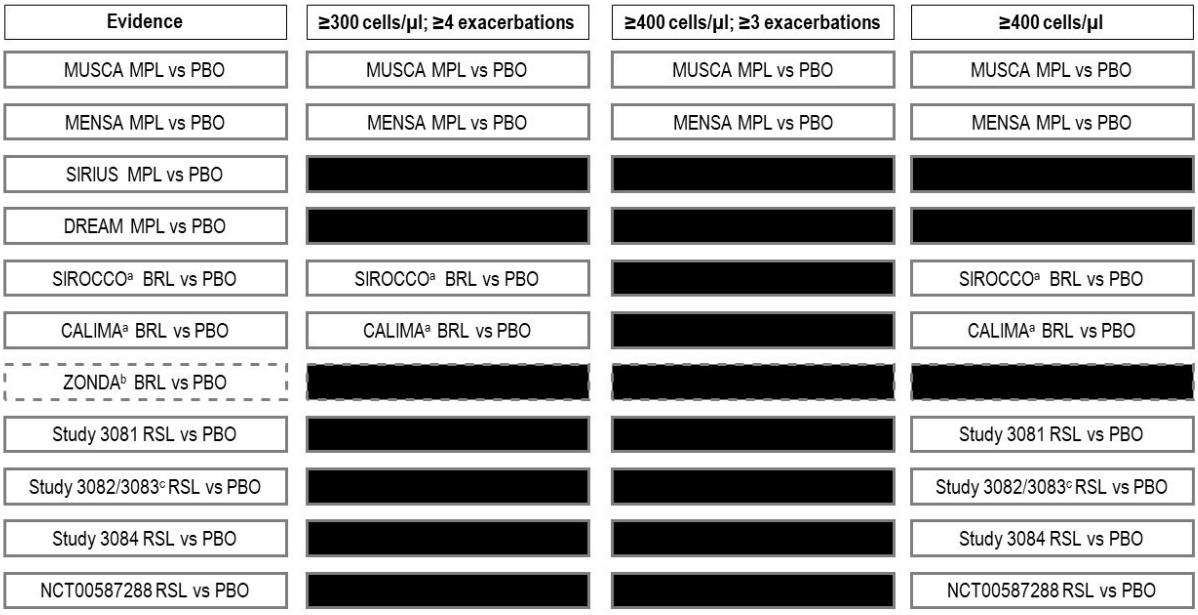
(2019)[2] (Section 3.2.3), and positioned this ITC as the key comparative efficacy data for mepolizumab versus benralizumab and reslizumab. The ITC compared the efficacy of mepolizumab, reslizumab and benralizumab at the approved doses (per summary of product characteristics [SmPC]), for people with severe eosinophilic asthma aged ≥12 years stratified by baseline eosinophil counts of ≥150, ≥300 and ≥400 cells/µl. The latter two counts were of closest relevance to this appraisal. Nine RCTS (reported in 11 publications) were included in the ITC (Figure 1). Of the 11 publications, two reported pooled analyses: one a pooled analysis of the benralizumab studies SIROCCO and CALIMA,[14] and two a pooled analysis of the two reslizumab studies (Study 3082/3083), which provided patient data for the endpoint exacerbations requiring hospitalisations/emergency department visits (all patients had GINA step 4/5 therapy and ≥2 exacerbations in the prior year).

Figure 1 shows which of the identified studies reported data for the following subgroups relevant to this appraisal:

- **current recommendation (TA431)** blood eosinophil count ≥300 cells/µl and ≥4 exacerbations in the previous 12 months (Section 3.2.1) (include for reference only);
- blood eosinophil count ≥400 cells/µl and ≥3 exacerbations in the previous 12 months (Section 3.2.2); and,
- blood eosinophil count ≥400 cells/µl (Section 3.2.3).

The available evidence is discussed in context of these subgroups.

Figure 1. Evidence overview stratified by blood eosinophil count



Abbreviations: BRL, benralizumab; CS, company submission; ITT, intention to treat; MPL, mepolizumab; PBO, placebo; RSL, reslizumab; TA, technology appraisal; vs, versus

Notes:

ZONDA was not specifically noted as an included study but it was discussed in the evidence summary reported by the company in Section of the CS (Document B)

Rationale for the exclusion of studies in black is discussed in the narrative below

[a] Study results for SIROCCO (Bleecker 2016[12]) and CALIMA (FitzGerald 2016[13]) also reported in pooled analysis (FitzGerald 2018[14])

[b] ZONDA not formally included but referred to in Section B.3.6.16 of the CS in context of the evidence base presented in TA565

[c] Study results for Study 3082/3083 reported in Castro 2015[17] and Brusselle 2017[18]

Source: MUSCA (Chupp 2017[9]); MENSA (Ortega 2014[10]); SIRIUS (Bel 2014[21]); DREAM Pavord 2012[11]); CALIMA (FitzGerald 2016[13]); SIROCCO (Bleecker 2016[12]); Study 3081 (Bjermer 2016[16]); Study 3082/3083 (Castro 2015[17], Brusselle 2017[18]); Study 3084 (Corren 2016[19]); NCT00587288 (Castro 2011[20])

3.2.1. Blood eosinophil count ≥300 cells/μL and ≥4 exacerbations

Current recommendation (per TA431):

Mepolizumab, as an add-on to optimised standard therapy, is recommended as an option for treating severe refractory eosinophilic asthma in adults, only if: the person has agreed to and followed the optimised standard treatment plan; and the **blood eosinophil count has been recorded as ≥300 cells/μl and the person has had ≥4 exacerbations needing systemic corticosteroids in the previous 12 months**, or has had continuous OCS of at least the equivalent of prednisolone 5 mg per day over the previous six months

This population was previously considered by NICE in TA431 and later in TA565. The company did not submit new clinical trial evidence for adults with blood eosinophil count ≥300 cells/μl and ≥4 exacerbations needing systemic corticosteroids in the previous 12 months. Despite limitations with the systematic review methods (Section 3.1), and a lack of clarity in the reporting of the study identification and data, the ERG was reasonably confident based on its own broader scrutiny of other published systematic reviews and guidelines that there was no new evidence which may alter existing recommendations.

Four RCTs reported data for this subgroup (benralizumab – SIROCCO and CALIMA; mepolizumab – MENSA and MUSCA). For this subgroup, the company presented data comparing mepolizumab with placebo during clarification (Appendix C, Table 22), and comparing mepolizumab with benralizumab in the CS (Appendix C, Table 20 and Table 21).

- **Mepolizumab vs benralizumab:** Mepolizumab significantly reduced the rate of clinically significant exacerbations compared with benralizumab (rate ratio 0.61 (95% CI 0.37, 0.99; p=0.047). For exacerbations requiring ED visits/hospitalizations, no significant difference was observed between the two groups. Mepolizumab was associated with greater improvements in change from baseline ACQ scores compared with benralizumab (difference: –0.40 [95% CI: –0.76, –0.03]; p=0.035). No difference observed in lung function (change from baseline in pre-bronchodilator FEV_1) between the two groups.
- **Mepolizumab vs reslizumab:** No data available.
- **Benralizumab vs reslizumab:** No data available.

Given the existing NICE recommendation, the ERG was satisfied that these data were aligned with data presented in previous TAs and did not scrutinize the data for this subgroup further. The ERG instead focused its critique on the subgroup of adults with baseline eosinophils ≥400 cells/μl and ≥3 severe exacerbations needing corticosteroids in the previous 12 months (Section 2.1): i.e. the subgroup of the severe asthma population reimbursed for reslizumab and benralizumab, but not currently reimbursed for mepolizumab.

3.2.2. Blood eosinophil count ≥400 cells/μL and ≥3 exacerbations

Add-on recommendation to align with TA565

Mepolizumab, as an add-on to optimised standard therapy, is recommended as an option for treating severe refractory eosinophilic asthma in adults, only if: the person has agreed to and followed the optimised standard treatment plan; and the blood eosinophil count has been recorded as ≥300 cells/μl and the person has had ≥4 exacerbations needing systemic corticosteroids in the previous 12 months, or has had continuous OCS of at least the equivalent of prednisolone 5 mg per day over the previous six months or the **blood eosinophil count has been recorded as ≥400 cells/μl with ≥3 exacerbations needing systemic corticosteroids in the past 12 months**

For this subgroup, the company provided data comparing mepolizumab with placebo from two RCTs (MENSA and MUSCA) during clarification (clarification response A11). The company also provided an analysis including the 75 mg IV dose of mepolizumab from MENSA and DREAM during clarification (clarification response A11). Baseline characteristics are provided in Table 2 and summary results for the rate of clinically significant exacerbations in Table 3. Data for this subgroup were, however, inconsistently available for the comparators (benralizumab and reslizumab), in part due to redaction in previous appraisals meaning it was not possible to estimate effectiveness relative to benralizumab or reslizumab.

Table 2. Subgroup baseline characteristics: subgroup ≥400 cells/μL and ≥3 exacerbations needing corticosteroids in the previous 12 months

	MPL 100 mg SC[a]	MPL 100 mg SC / MPG 75 mg[b]	PBO[a]
N (Total ITT)	[redacted]	[redacted]	[redacted]
n (subgroup)	[redacted]	[redacted]	[redacted]
Age years, mean (SD)	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]
BMI kg/m^2, mean (SD)	[redacted]	[redacted]	[redacted]
Total exacerbations			
3, n (%)	[redacted]	[redacted]	[redacted]

	MPL 100 mg SC[a]	MPL 100 mg SC / MPG 75 mg[b]	PBO[a]
4, n (%)	[redacted]	[redacted]	[redacted]
≥4, n (%)	[redacted]	[redacted]	[redacted]
Total exacerbations that required ER visits and/or hospitalisation			
0, n (%)	[redacted]	[redacted]	[redacted]
1, n (%)	[redacted]	[redacted]	[redacted]
2, n (%)	[redacted]	[redacted]	[redacted]
3, n (%)	[redacted]	[redacted]	[redacted]
4, n (%)	[redacted]	[redacted]	[redacted]
≥4, n (%)	[redacted]	[redacted]	[redacted]
Total exacerbations that required hospitalisation, n			
0, n (%)	[redacted]	[redacted]	[redacted]
1, n (%)	[redacted]	[redacted]	[redacted]
2, n (%)	[redacted]	[redacted]	[redacted]
3, n (%)	[redacted]	[redacted]	[redacted]
4, n (%)	[redacted]	[redacted]	[redacted]
≥4, n (%)	[redacted]	[redacted]	[redacted]
Duration of asthma, mean (SD)	[redacted]	[redacted]	[redacted]
12 months prior to Visit 1 elevated peripheral blood eosinophil count ≥300			
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
At Visit 1 elevated peripheral blood eosinophil count ≥150 cells/µl[c]			
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Maintenance OCS use, n (%)	[redacted]	[redacted]	[redacted]
BL OCS daily dose[d] (prednisolone equivalent), mean (SD)	[redacted]	[redacted]	[redacted]
Baseline Blood eosinophils (GI/L), Geo mean (Std Logs)	[redacted]	[redacted]	[redacted]

Abbreviations: BL, baseline; BMI, body mass index; ER, emergency room; ITT, intention to treat; IV intravenous; MPL, mepolizumab; OCS, oral corticosteroids; PBO, placebo; SC, subcutaneous; SD, standard deviation

Notes:

[a] MUSCA and MENSA studies

[b] MUSCA< MENSA and DREAM studies

[c] Elevated peripheral blood eosinophil count ≥150 cells/µl at Visit 1 determined from laboratory data collected at this visit

[d] Daily dose derived for participants that indicated they were on regular maintenance OCS at baseline

Source: Clarification Response Table A11.1

Table 3. Subgroup analysis of clinically significant exacerbations: subgroup ≥400 cells/µL and ≥3 exacerbations needing corticosteroids in the previous 12 months

	MPL 100 mg SC	MPL 100 mg SC / MPL 75 mg IV	PBO
N (Total, ITT)	467	811	624
Subgroup ≥400 cells/µL and ≥3 exacerbations by trial:			
MENSA, n[a]	[redacted]	[redacted]	[redacted]
Exacerbation rate / year	[redacted]	[redacted]	[redacted]
Rate ratio MPL/PBO (95% CI)[b]	[redacted]	[redacted]	
MUSCA, n[a]	[redacted]	[redacted]	[redacted]
Exacerbation rate / year	[redacted]	[redacted]	[redacted]
Rate ratio MPL/PBO (95% CI)[b]	[redacted]	[redacted]	
DREAM, n[a]	NA	[redacted]	[redacted]
Exacerbation rate / year	NA	[redacted]	[redacted]
Rate ratio MPL/PBO (95% CI)[b]		[redacted]	
Meta-analysis (MENSA/MUSCA/DREAM) , n[a]	[redacted]	[redacted]	[redacted]
Rate ratio MPL/PBO (95% CI)[c]	[redacted]	[redacted]	

Abbreviations: BMI, body mass index; ER, emergency room; FEV_1, forced expiratory volume in one second; ITT, intention to treat; IV, intravenous; MPL, mepolizumab; OCS, oral corticosteroids; PBO, placebo; SC, subcutaneous; SD, standard deviation

Notes:

[a] Number of subjects with analysable data

[b] Analysis performed using a negative binomial regression model with covariates of treatment group, region, exacerbations in the year prior to the study (as an ordinal variable), baseline OCS (yes, no)) and baseline percent predicted FEV_1 with logarithm of time on treatment as an offset variable

[c] Inverse variance weighed fixed effects meta-analysis

Source: Clarification Response Table A11.2: MUSCA (Chupp 2017[9]); MENSA (Ortega 2014[10]); DREAM (Pavord, 2012[11])

- **Mepolizumab vs benralizumab:** No data available.
- **Mepolizumab vs reslizumab:** No data available.
- **Benralizumab vs reslizumab:** No data available.

Although the company were unable to conduct an analysis comparing mepolizumab with benralizumab or reslizumab in this subgroup, it did present an analysis for the broader subgroup (blood eosinophil count ≥400 cells/µL) from Busse et al. (2019)[2] (refer to Section 3.2.3), and also for a more restricted subgroup blood eosinophil count of ≥400 cells/µl and who have had ≥4 severe asthma exacerbations in the previous 12 months (refer to Appendix D).

3.2.3. Blood eosinophil count ≥400 cells/µL

For this subgroup, the company provided comparative effectiveness data was based on a published ITC (Busse et al., 2019).[2]

3.2.3.1. Summary of indirect treatment comparison

Table 4 provides an overview of the included studies and number of participants that contributed data for different outcomes.

Table 4. Studies included in the ITC for each outcome for adults with blood eosinophils of ≥400 cells/µl

Outcomes	Mepolizumab	Benralizumab	Reslizumab
Clinically significant exacerbations	MENSA (n=173) MUSCA (n=182)	SIROCCO and CALIMA (n=604)[b]	Study 3082 (n=489) and Study 3083 (n=464)
ACQ		SIROCCO and CALIMA (n=604)[b]	NCT00587288 (n=106), Study 3081 (n=211), Study 3082 (n=489), Study 3083 (n=464) , Study 3084 (n=96)
Exacerbations requiring ED visit/hospitalization		N/A*	Studies 3082 (n=489) and Study 3083 (n=464)[a]
FEV1		SIROCCO and CALIMA (n=604)[b]	NCT00587288 (n=106), Study 3081 (n=211), Study 3082 (n=489), Study 3083 (n=464), Study 3084 (n=96)

Abbreviations: ACQ score, Asthma Control Questionnaire; ED, emergency department; FEV_1, Forced expiratory volume in one second

Notes:

Not enough data were available to measure exacerbations requiring ED visit/hospitalization

[a] Study results for Study 3082 and 3083 for this outcome reported in [18]

[b] Study results for SIROCCO (Bleecker 2016[12]) & CALIMA (FitzGerald 2016[13]) also reported in pooled analysis (FitzGerald 2018[14])

Source: MUSCA (Chupp 2017[9]); MENSA (Ortega 2014[10]); CALIMA (FitzGerald 2016[13]); SIROCCO (Bleecker 2016[12]); Study 3081 (Bjermer 2016[16]); Study 3082/3083 (Castro 2015[17]), (Brusselle 2017[18]); Study 3084 (Corren 2016[19]); NCT00587288 (Castro 2011[20])

The ERG noted that several potentially relevant studies were omitted from the ITC compared with the previous TAs. These studies included ZONDA, SIRIUS and DREAM. During clarification (clarification question A3b), the company stated that the ZONDA and SIRIUS trials were designed to measure the reduction in severe asthma patients dependent on maintenance OCS for mepolizumab and benralizumab, respectively. Hence, their study design and endpoints prevented them being included in the ITC. The ERG considered this a reasonable rationale for

the omission of ZONDA and SIRIUS from the ITC. The company clarified that the 75 mg treatment arms from DREAM and MENSA were omitted from the ITC to ensure that the interventions evaluated reflected routine clinical practice. While the company did not provide ITC results including DREAM, during clarification it provided a further set of meta-analyses which indicated that excluding mepolizumab 75 mg dose data from the ITC had minimal effect on efficacy results for the subgroup with eosinophil count ≥300 cells per microlitre and ≥4 exacerbations in the past year (MPL 100 mg SC vs PBO rate ratio (RR) [redacted] and MPL 100 mg SC / MPL 75 mg IV RR [redacted]) clarification response A11, Table A11.2). The ERG noted inconsistency between the results reported for reduction in exacerbation rate for the subgroup with blood eosinophil count ≥300 cells per microlitre and ≥4 exacerbations in the previous year using the 100 mg dose in the ITC, and the new meta-analysis for the same dose provided by the company (Tables E10 & Table A11.2, respectively). However, the ERG acknowledged the slight variation in population between the ITC and the meta-analysis provided in Table A11.2 of the clarification response; i.e. ≥300 cells per microlitre and ≥4 exacerbations in the past year (company meta-analysis) vs ≥300 cells per microlitre, ≥4 exacerbations in the past year and ACQ ≥1.5 (Busse et al., 2018; Table E10), that could account for the inconsistency in results.

Baseline data for subgroups of participants in included trials were inconsistently available, in part due to redaction in previous appraisals. This precluded the ERG from assessing the transitivity in the ITC and any potential effect modification.

There were no restrictions on study timeframe or duration. Based on clinical advice, the ERG was of the opinion that the study duration ranging from 15 to 56 weeks has a minor effect on the ITC results.

The outcomes of the ITC included exacerbation requiring treatment with OCS; exacerbation requiring an ED visit/hospitalization; ACQ score; and change from baseline pre-bronchodilator FEV_1. The ERG noticed that steroid reduction was among the outcomes missing from the ITC since none of the studies included in the ITC allowed for this comparison. However, clinical advice to the ERG suggested that a reduction in exacerbations may also imply a reduction in steroid use so the ERG does not consider this an issue, rather a point of discrepancy versus the prior TAs. The ERG considered that the outcomes included were appropriate to the decision problem presented.

Indirect treatment effect estimates were produced by using the two-step Bucher method. Pairwise comparisons vs placebo were meta-analysed and 95% CIs, I^2 scores, and p-values reported for each outcome measure and treatment. Generally, the reported I^2 scores were below 40% which indicated limited heterogeneity between the studies, hence fixed effect estimates were used for the comparisons. The only exception was the heterogeneity score between SIROCCO and CALIMA for exacerbation for which the I^2 was high (73–86%). In this case random effect estimation was employed. Inverse variance weighting and DerSimonian and Laird methods were used for fixed and random effects meta-analyses of each treatment versus placebo, respectively. However, heterogeneity estimates were only presented for overall populations rather than for the subgroup of interest. The results of an unadjusted comparison with placebo were provided as a sensitivity analysis for the ITC; this comparison does not put any restriction for baseline blood eosinophil counts or ACQ scores and included all the ITT population for all treatments. The results of the sensitivity analysis showed significant improvement in all the outcome measures. The ERG was broadly satisfied with the statistical methods used for the ITC.

Table 5 provides the ITC results for the subgroup of adults with baseline blood eosinophils ≥400 cells/µl from the CS.

Table 5. Summary of the ITC results for baseline blood eosinophils ≥400 cells/µl (Busse et al., 2019)

	MPL vs BRL	MPL vs RSL	RSL vs BRL
Rate of clinically significant exacerbations	MPL reduces the rate significantly (RR 0.55, 95% CI [0.35, 0.87]; p=0.011)	MPL reduces the rate significantly (RR 0.55, 95% CI [0.36, 0.85]; p=0.007)	No difference (RR 1.00, 95% CI [0.71, 1.40])
Rate of exacerbations requiring ED visits/hospitalizations	No data available	MPL is not significantly worse (RR 1.24, 95% CI [0.32, 4.77])	No data available
Patient-reported asthma control (ACQ score)	MPL has greater improvement from baseline (difference: –0.36 95% CI [–0.66, –0.05]; p=0.023)	MPL has greater improvement from baseline (difference: –0.39 95% CI [–0.66, –0.12]; p=0.004)	BRL is not significantly better (difference: 0.04, 95% CI [−0.15, 0.23])
Change from baseline in pre-bronchodilator FEV_1	MPL is not significantly worse (difference: -0.05, 95% CI [-0.18, 0.09])	MPL is not significantly better (difference: 0.06, 95% CI [-0.05, 0.17])	BRL is more effective (difference: 0.11, 95% CI [0.01, 0.20]; p=0.025)

Abbreviations: ACQ score, Asthma Control Questionnaire; BRL, benralizumab; CI, confidence interval; ED, emergency department; FEV_1, Forced expiratory volume in one second; MPL, mepolizumab; RR, Rate Ratio; RSL, reslizumab; vs, versus

Table 6 represents the treatment ranks and p-values for mepolizumab, reslizumab and benralizumab for each endpoint for the patients with blood eosinophil counts of ≥400 cells/µl.

Table 6. Summary of treatment ranks and p values for mepolizumab, reslizumab and benralizumab for each endpoint in adults with a blood eosinophil count of ≥400 cells/µl

	Treatment rank (p-value)		
	1	2	3
Clinically significant exacerbations			
≥400 cells/µL	MPL (0.997)	RSL (0.504)	BRL (0.499)
Unadjusted comparison[a]	MPL (0.917)	RSL (0.699)	BRL (0.384)
Exacerbations requiring ED visits/hospitalisations			
≥400 cells/µL	RSL (0.810)	MPL (0.681)	–
Unadjusted comparison[a]	MPL (0.952)	RSL (0.483)	BRL (0.477)
Asthma control score			
≥400 cells/µL	MPL (0.995)	BRL (0.552)	RSL (0.453)
Unadjusted comparison[a]	MPL (0.970)	RSL (0.519)	BRL (0.511)
Pre-bronchodilator FEV_1			
≥400 cells/µL	BRL (0.915)	MPL (0.697)	RSL (0.389)
Unadjusted comparison[a]	BRL (0.744)	RSL (0.716)	MPL (0.540)

Abbreviations: BRL; benralizumab, ED; emergency department, MPL; mepolizumab, RSL; reslizumab; FEV1, Forced expiratory volume in one second

Notes:

[a] An unadjusted comparison was also performed as a sensitivity analysis for the ITC, in which the ITT populations for all treatments, uncontrolled for baseline blood eosinophil counts or ACQ scores, were used to compare the effect of treatment on the 4 end points; this analysis is referred to as the unadjusted comparison.

3.2.3.2. Critique of the ITC conducted by the company

Whilst Busse et al (2019)[2] used Bucher's adjusted indirect comparison methodology, a previous ITC (Bourdin et al, 2020[22]) used population matching to compare benralizumab with mepolizumab (TA565). Bourdin et al. argued NMA was not feasible due to heterogeneity between patient populations hence used a matching adjusted indirect comparison (MAIC) approach.

The debate between these alternative ITC methodologies was the subject of correspondence between Busse et al. and Bourdin et al. in the literature (Bourdin, 2019[23] and Gunsoy 2019[24]). Bourdin et al. noted that Busse et al. included only licensed treatments, made no adjustment for treatment effect modifiers, and excluded the DREAM study. In response, Busse et al. noted that Bourdin et al included licensed and unlicensed treatments, omitted a key treatment effect modifier, and excluded the MUSCA study. The NICE Committee in TA565 also declared: "the use of MAIC instead of NMA had not been adequately justified". The ERG noted that neither study found a significant difference between mepolizumab and benralizumab. The ERG also

noted that NMA using meta-regression may also have been a feasible alternative to Bucher's method given there are multiple studies per treatment comparison.

The ERG regarded that the methods used for the ITC and the interpretation of the results were broadly appropriate. The ERG further regarded that mepolizumab generally provided similar, if not better, effectiveness as compared to benralizumab and reslizumab within the focal subgroup. However, the ERG noted several considerations in terms of the ITC's methods and results which are as follows.

Several potentially relevant trials were excluded from the ITC. These trials included ZONDA, SIRIUS, DREAM and 75 mg dose mepolizumab treatment arm in MENSA. The exclusion of ZONDA and SIRIUS does not affect the final result of the ITC as their primary outcome is reduction of the OCS consumption. However, the ERG was unable to fully assess the effect of the exclusion of the DREAM study and the exclusion of the 75 mg IV treatment arm from MENSA on the final efficacy result due to the lack of information provided by the company.

The primary focus of the ITC was based on the patients with blood eosinophils count of ≥400 cells/μl. However, the company is seeking to broaden the eligible population for mepolizumab to patients with a blood eosinophil count of ≥400 cells per microliters who have had ≥3 severe asthma exacerbations in the previous 12 months, which is the current eligible population for benralizumab based on TA565. While the company did not present data for the specific subgroup of interest, it did present analyses for the broader subgroup of participants with blood eosinophil count ≥400 cells/μl and also for a more restricted subgroup (blood eosinophil count ≥400 cells/μl and ≥4 severe asthma exacerbations in the previous 12 months [Appendix B]). In respect of the former, although the subgroup was not exactly aligned to the recommendation extension, trial inclusion criteria these participants all had at least one (reslizumab) or two (mepolizumab and benralizumab) severe exacerbations in the previous 12 months. In principle, therefore, the ERG considered that the broader subgroup was closer than not. While it was not possible to comprehensively assess this in respect of the potential modification of treatment effect, the ERG considered that it would not substantively alter the conclusion regarding similar or greater effectiveness. Overall, the ERG considered this to be a reasonable approach.

3.3. Summary and critique of the evidence on safety submitted by the company

In clinical studies in subjects with severe refractory eosinophilic asthma, the most commonly reported adverse reactions during treatment were headache, injection site reactions and back pain[25]. The frequency of adverse reactions is provided in Table 7[25].

The company also presented safety data for mepolizumab in severe refractory eosinophilic asthma patients (n=998) treated for a median of 2.8 years (range: four weeks to 4.5 years) in open-label extension studies (COLUMBA[26] and COSMEX[27]) which was similar to that observed in the placebo-controlled studies (refer to Appendix F of the CS). The ERG noted that mepolizumab appeared to be generally well-tolerated in severe eosinophilic asthma patients.

Table 7 Frequency of adverse reactions by system organ class

System organ class	Adverse reactions	Frequency[a]
Infections and infestations	Lower respiratory tract infection Urinary tract infection Pharyngitis	Common
Immune system disorders	Hypersensitivity reactions (systemic allergic)[b] Anaphylaxis[c]	Common Rare
Nervous system disorders	Headache	Very common
Respiratory, thoracic and mediastinal disorders	Nasal congestion	Common
Gastrointestinal disorders	Abdominal pain upper	Common
Skin and subcutaneous tissue disorders	Eczema	Common
Musculoskeletal and connective tissue disorders	Back pain	Common
General disorders and administration site conditions	Administration-related reactions (systemic non-allergic)[d] Local injection site reactions Pyrexia	Common

Abbreviations: AEs, adverse events

Notes:

[a] Frequency of AEs is defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

[b] Systemic reactions including hypersensitivity have been reported at an overall incidence comparable to that of placebo

[c] From spontaneous post-marketing reporting

[d] The most common manifestations associated with reports of systemic non-allergic administration-related reactions were rash, flushing and myalgia; these manifestations were reported infrequently and in <1% of subjects receiving mepolizumab 100 mg subcutaneously

The company presented summaries of key safety events from the included trials (CS, Document B, Section B.3.10). The included trials were broadly similar to those included in the previous appraisals (TA431[6], TA479[7], TA565[1]: comparison with placebo indicated numerically similar or fewer AEs for mepolizumab, reslizumab, and benralizumab (Table 8). In general, the ERG considered that there were no major differences between mepolizumab and the comparator drugs.

Table 8. Comparative summary of the safety profile for MPL, RSL, and BRL by study

	Dose	AEs %	Any drug-related AE %	Any SAE %	AE leading to discontinuation or study withdrawal %
MPL (MENSA, SIRIUS, DREAM)	MPL 100 mg SC	79	23	6	NR
	MPL 75 mg IV	83	18	10	NR
	PBO	82	16	15	NR
MPL (MUSCA)	MPL 100 mg SC	74	11	15	<1
	PBO	70	9	22	1
RSL (Study 3081)[a]	RSL 3.0 mg/kg	59	12	4	6
	PBO	63	8	1	10
RSL (Study 3082)	RSL 3.0 mg/kg	80	15	10	2
	PBO	85	15	14	3
RSL (Study 3083)	RSL 3.0 mg/kg	76	15	10	3
	PBO	87	12	10	4
RSL (Study 3084)	RSL 3.0 mg/kg	55	7	4	7
	PBO	74	16	4	12
BRL (SIROCCO)	BRL 30 mg Q8W	71	NR	13	2
	PBO	76	NR	12	<1
BRL (SIROCCO)	BRL 30 mg Q8W	75	13	9	2
	PBO	78	8	14	<1
BRL (ZONDA)	BRL 30 mg Q8W	75	NR	10	4
	PBO	83	NR	19	3

Abbreviations: AEs, adverse events; BRL, benralizumab; IV, intravenous; MPL, mepolizumab; NR, not reported; PBO, placebo; RSL, reslizumab; SAEs, serious adverse events; SC, subcutaneous

Notes:

[a] Data reported for two of three treatment arms. The third treatment arm was RSL 0.3 mg/kg

Source: CS, Document B, Section B.3.10 – MUSCA (Chupp 2017[9]); MENSA (Ortega 2014[10]); SIRIUS (Bel 2014[21]); DREAM Pavord 2012[11]); CALIMA (FitzGerald 2016[13]); SIROCCO (Bleecker 2016[12]); ZONDA (Nair, 2017[28]); Study 3081 (Bjermer 2016[16]); Study 3082/3083 Castro 2015[17]; Brusselle 2017[18]); Study 3084 (Corren 2016[19])

The company also referenced the meta-analysis carried out in the Cochrane review[15] which found no excess serious adverse events (SAEs) with any anti-IL-5 pathway-directed treatment compared with placebo (Table 9).

Table 9. Serious adverse events

Comparison	Study references	N studies (N participants)	RR (95% CI) [Random Effects, M-H]
MPL SC vs PBO	Chupp 2017[9]; Ortega 2014[10]	2 (936)	0.63 (0.41, 0.97)
MPL IV vs PBO	Haldar 2009[29]; Pavord 2012[11]; Ortega 2014[10]	3 (751)	0.59 (0.37, 0.94
RSL IV vs PBO	Bjermer 2016[16]; Castro 2015[17]; Corren 2016[19]	4 (1,656)	0.79 (0.56, 1.12)
BRL SC vs PBO	Bleecker 2016[12]; Castro, 2014[30]; FitzGerald 2016[13]; Park, 2016[31]	4 (2,648)	0.81 (0.66, 1.01)

Abbreviations: BRL, benralizumab; CI, confidence interval; IV, intravenous; M-H, Mantel-Haenszel; MPL, mepolizumab; N, number of; PBO, placebo; RR, risk ratio; RSL, reslizumab; SC, subcutaneous; vs, versus

Source: Farne et al., 2017[15]

3.3.1. Blood eosinophil count ≥300 cells/μL and ≥4 severe exacerbations

No comparative data in respect of safety outcomes for mepolizumab compared with benralizumab or reslizumab or for benralizumab or reslizumab were presented in the CS for this subgroup of participants with blood eosinophil count ≥300 cells/μL and ≥4 severe exacerbations in the previous 12 months in the CS.

3.3.2. Blood eosinophil count ≥400 cells/μL and ≥3 severe exacerbations

No comparative data in respect of safety outcomes for mepolizumab compared with benralizumab or reslizumab were presented in the CS for this subgroup of participants with baseline eosinophils ≥400 cells/μL and ≥3 severe exacerbations needing corticosteroids in the previous 12 months in the CS.

3.3.3. Blood eosinophil count ≥400 cells/μL

Safety data for reslizumab compared placebo in this population were available in the individual study publications (Table 8 and Table 9).[16,17,19]

No comparative data in respect of safety outcomes for mepolizumab compared with benralizumab or reslizumab were presented in the CS for this subgroup of participants with baseline eosinophils ≥400 cells/μL and ≥3 severe exacerbations needing corticosteroids in the previous 12 months in the CS.

3.4. Overall summary

Evidence indicates that there is a low risk that mepolizumab is less effective than other available anti-IL5 treatments for severe eosinophilic asthma as recommended by NICE.

4. COST-EFFECTIVENESS

4.1. Summary: ERG's critique of the cost-effectiveness evidence submitted

4.1.1. Population and comparator

The company submitted a cost comparison over a one-year time horizon comparing mepolizumab 100 mg as an add on to optimised standard therapy to reslizumab and benralizumab for the treatment of severe refractory eosinophilic asthma in adults. The ERG noted that there may be some uncertainty surrounding the appropriateness of a one-year time horizon given that differences in dosing frequency and administration between treatments are likely to persist over time. As an exploratory analysis, the ERG conducted a scenario analysis which increases the time horizon to 10 years (see Section 4.1.6.1 for results).

The company is seeking to broaden/extend the NICE recommendation for mepolizumab to include patients with a blood eosinophil count of ≥400 cells per microlitre and who have had ≥3 severe asthma exacerbations in the previous 12 months. Reslizumab and benralizumab were included as comparators within the cost comparison on the basis that these anti-IL-5 treatment options are currently recommended by NICE for use in this subgroup of patients. The company noted reslizumab to be the primary comparator, however clinical advice to the ERG suggested that benralizumab is likely to be displaced in practice. Results versus both comparators have been provided in the cost comparison.

The assumption of comparable efficacy between treatments was based on an indirect comparison by Busse et al. (2019).[2] The analysis included nine placebo-controlled studies and treatments were assessed for primary outcomes which included exacerbation requiring treatment with OCS; exacerbation requiring an ED visit/hospitalization; ACQ score; and change from baseline pre-bronchodilator FEV_1. The ERG noted that several potentially relevant studies (ZONDA and SIRIUS) were omitted from the analysis. Following clarification from the company, these were identified as OCS reduction studies and therefore not considered. Based on the ITC, mepolizumab appeared to demonstrate improved efficacy versus both comparators for clinically significant exacerbations and asthma control; however, benralizumab was considered superior to mepolizumab for change from baseline in pre-bronchodilator FEV1 (see Table 5 and Table 6 in Section 3.3.3). While the company did not present data for the specific subgroup of interest, it did present analyses for the broader subgroup of participants with baseline eosinophil count ≥400 cells/μl. Based on inclusion criteria these participants all had at least one (reslizumab) or two (mepolizumab and benralizumab) severe exacerbations in the previous 12 months, so

although the subgroup was not exactly aligned to the recommendation extension, in principle it was closer than not. While it was not possible to comprehensively assess this in respect of the modification of treatment effect, the ERG considered that it would not substantively alter the conclusion regarding similar or greater effectiveness. Overall, the ERG considered this to be a reasonable approach.

4.1.2. Technology acquisition costs

Medicine acquisition costs were included in the analysis for mepolizumab 100 mg solution for injection and pre-filled pen/syringe formulations. All mepolizumab formulations were priced at parity (list price of £840 per 100 mg dose). The company submitted a PAS for mepolizumab of [redacted] per 100 mg dose (a reduction of [redacted] on the list price). The cost comparison did not include mepolizumab 75 mg. However, clinical advice to the ERG noted that the 75 mg dose is considered to be bio-equivalent to the 100 mg dose. For benralizumab medicine acquisition costs were based on a 30 mg pre-filled pen/syringe (list price of £1,955 per 30 mg dose) whilst reslizumab costs have been estimated based on an average patient weight of 75 kg (3 mg/kg) and a list price of £499.99 and £124.99 for the 100 mg and 25 mg vials respectively.

Regarding dose frequency, mepolizumab 100 mg was administered every four weeks, reslizumab 3 mg/kg every four weeks and benralizumab 30 mg every eight weeks [3 × 4 weekly doses followed by eight-weekly dosing]. Based on the SmPC for each treatment and a review of benralizumab TA565 and reslizumab TA479, the ERG confirmed that these dosing schedules are appropriate. The company presented the results for the cost comparison using the list prices for comparator treatments and including the PAS price for mepolizumab. The ERG replicated all of the company's analyses and conducted additional scenario analyses using the appropriate PAS prices for all treatments (see confidential PAS appendix).

4.1.3. Administration and monitoring costs

Within the analysis all treatments were assumed to require nurse administration and monitoring for the first three doses (see Section B.4.2.3 of the CS). The company assumed that one hour of monitoring was required, involving 15 minutes of specialist nurse time. This assumption was justified by the company on the basis that it was accepted within the previous NICE appraisal for mepolizumab TA431. Clinical advice to the ERG confirmed that anti-IL-5 treatments are likely to have similar monitoring requirements, though there may be additional monitoring requirements associated with reslizumab, particularly for the first three doses, due to the requirement of cannulation (as noted in reslizumab TA479). However, the company's base case approach

could be considered conservative, as increasing monitoring costs for reslizumab would lead to an increase in incremental savings for mepolizumab. Overall, the ERG does not consider monitoring costs to be a key driver of the incremental results.

For mepolizumab and benralizumab pre-filled pen/syringe formulations, the analysis assumed that the first three doses would be administered and under specialist nurse supervision, to account for self-administration training. The company estimated the cost per specialist nurse hour to be £100 (based on mepolizumab TA431). The ERG considered this to be somewhat dated as this cost was calculated from PSSRU 2014. The ERG has amended the company's analysis using a more recent PSSRU cost of £113 (see Section 4.1.5).

For mepolizumab, the company estimated administration costs using three different assumptions.

- Mepolizumab 100 mg SC solution for injection: It was assumed that administration was carried out by a specialist nurse for all 13 doses. This analysis was associated with administration costs of £330 per year due to the time required for preparation and administration at each visit (10 minutes). The ERG acknowledges that given the availability of the pre-filled pen/syringe formulation, the assumption that all patients will require nurse administration is considered conservative.
- Mepolizumab 100 mg (pre-filled pen/syringe): It was assumed that administration was carried out by a nurse specialist for all 13 doses. Administration costs were estimated to be £207 per year on the basis that the pre-filled pen/syringe formulation does not require reconstitution but administration time only, which was assumed to be five minutes. Clinical advice to the ERG confirmed five minutes to be a reasonable administration time for the pre-filled pen/syringe formulation.
- Mepolizumab 100 mg (pen/syringe)-self-administration: It was assumed that all patients receiving mepolizumab will self-administer. The cost of administration for the first year was estimated to be £113, which included monitoring and administration costs for the first three initial doses only. No administration costs are applied after the first year of treatment. Thereafter patients were assumed to self-administer at home.

Estimating administration costs for mepolizumab based on different administration assumptions is helpful as there may be some uncertainty surrounding which formulation of mepolizumab is

likely to be predominantly used in practice and the proportion of patients self-administering via the pen/syringe.

4.1.4. Adverse event costs

No treatment related AE costs were included in the analysis. The company did not justify their decision to exclude these costs, however clinical advice to the ERG noted that mepolizumab appeared to have a similar safety profile to benralizumab and reslizumab.

As previously mentioned, OCS use was not considered as an outcome within the ITC. This may introduce some uncertainty surrounding comparable efficacy between treatments with respect to steroid sparing effect. For completeness, the ERG conducted a scenario analysis which assumed a proportion of mepolizumab patients would incur healthcare costs associated with continuous OCS use (see Section 4.1.6.1 for results).

4.1.5. Company cost comparison model

The inputs and assumptions used to estimate the base case results are presented in Section B.4.1, B.4.2.2 and B.4.2.3 of the CS. The costs were presented over a one-year time horizon and were not discounted. This is in line with NICE guidance for cost comparisons. No formal model was submitted by the company detailing calculations; however, the ERG was able to replicate results and create a model template using the company's assumptions. As previously noted in Section 4.1.3, the ERG updated and amended the company's base case analysis to correct minor discrepancies surrounding the estimation of medicine acquisition and healthcare resource use costs (Table 10). These amendments did not have a material impact on the results.

Table 10. ERG corrections

Errors within the CS	ERG amendments
BRL 30mg list price estimated to be £1,995	Amended to reflect BNF list price of £1,955
Specialist nurse cost per hour estimated to be £100 (based on PSSRU 2014)	Amended to reflect more recent PSSRU costs (£113)

Abbreviations: BNF, British national Formulary; BRL, benralizumab; CS, company submission; ERG, Evidence Review Group; PSSRU, Personal Social Services Research Unit

Based on the assumption of comparable efficacy between treatments, the cost comparison analysis did not include any efficacy parameters such as treatment response rates or discontinuation rates. The company assumed that all patients receiving mepolizumab, reslizumab and benralizumab responded to treatment and therefore did not require OCS

treatment. The ERG explored uncertainty within the company's analysis by conducting additional scenario analyses which investigated the impact of extending the time horizon to 10 years, used conservative administration assumptions for mepolizumab and included OCS related healthcare cost for mepolizumab only. The key results are presented and discussed in Section 4.1.6.1.

4.1.5.1. Company results

The base case cost comparison results were provided in Section B.4.3 of the CS; these results were updated by the company during clarification to include the updated administration cost (clarification response B1). It should be noted that the results presented below reflect the corrected results following clarification from the company. Therefore, these results differ to those reported in the CS. Results were provided using the list price for all treatments (Table 11), and using the appropriate PAS discount for mepolizumab (Table 12). The ERG also estimated results using the appropriate PAS discounts for both reslizumab and benralizumab (these results including PAS for all treatments are provided in a confidential appendix).

Table 11. Base case results (list prices all treatments)

Medicines	Acquisition costs	Administration costs	Total costs	Incremental savings vs RSL	Incremental savings vs BRL
MPL 100 mg powder for solution for injection (assumes patients require nurse admin for every dose)	£10,920	£330	£11,250	-£4,439*	-
MPL 100 mg solution for injection in pre-filled syringe or pen	£10,920	£207	£11,127	-£4,562*	-
MPL 100 mg solution for injection in pre-filled syringe or pen (assumes all patients self-administer from dose 3 onwards)	£10,920	£113	£11,033	-£4,656*	-
RSL 10 mg/mL concentrate for solution for infusion	£14,625	£1,064	£15,689	-	-
BRL 30 mg pre-filled syringe or pen (assumes all patients self-administer) vs MPL 100 mg (assumes patients require nurse admin for every dose)	£15,640	£113	£15,753	-	-£4,503*
BRL 30 mg pre-filled syringe or pen (vs MPL 100mg pre-filled syringe or pen)	£15,640	£160	£15,800	-	-£4,673*

Medicines	Acquisition costs	Administration costs	Total costs	Incremental savings vs RSL	Incremental savings vs BRL
BRL 30 mg pre-filled syringe or pen (self-administration) vs MPL 100mg pre-filled syringe or pen (self-administration)	£15,640	£113	£15,753	-	-£4,720*

Abbreviations: BRL, benralizumab; MPL, mepolizumab; RSL, reslizumab; vs, versus

Notes:

*Denotes incremental savings for MPL

Table 12. Base case results (including mepolizumab PAS)

Medicines	Acquisition costs	Administration costs	Total costs	Incremental savings vs RSL	Incremental savings vs BRL
MPL 100 mg powder for solution for injection (assumes patients require nurse admin for every dose)	[redacted]	£330	[redacted]	[redacted]	-
MPL 100 mg solution for injection in pre-filled syringe or pen	[redacted]	£207	[redacted]	[redacted]	-
MPL 100 mg solution for injection in pre-filled syringe or pen (assumes all patients self-administer from dose 3 onwards)	[redacted]	£113	[redacted]	[redacted]	-
RSL 10 mg/mL concentrate for solution for infusion	£14,625	£1,064	£15,689	-	-
BRL 30 mg pre-filled syringe or pen (assumes all patients self-administer) vs MPL 100 mg (assumes patients require nurse admin for every dose)	£15,640	£113	£15,753	-	[redacted]
BRL 30 mg pre-filled syringe or pen (vs MPL 100mg pre-filled syringe or pen)	£15,640	£160	£15,800	-	[redacted]
BRL 30 mg pre-filled syringe or pen (self-administration) vs MPL 100mg pre-filled syringe or pen (self-administration)	£15,640	£113	£15,753	-	[redacted]

Abbreviations: BRL, benralizumab; MPL, mepolizumab; RSL, reslizumab; vs, versus

Notes:

*Denotes incremental savings for MPL

4.1.6. ERG exploratory analyses

4.1.6.1. Scenario analyses conducted by the ERG

4.1.6.2. Time Horizon

There may be some uncertainty as to whether a one-year time horizon is sufficient to capture the key differences in costs between treatments over time. Based on a list price comparison for all treatments, which increased the time horizon to 10 years without discounting costs, mepolizumab 100 mg remained cost saving versus both benralizumab and reslizumab. For the comparison versus benralizumab administration costs for both treatments varied according to resource use assumptions. Over 10 years administration costs ranged from £113 to £2,533 for mepolizumab and £113 to £716 for benralizumab. In terms of medicine acquisition costs, mepolizumab resulted in lower total costs (£109,200 versus £130,985 for mepolizumab and benralizumab respectively) over 10 years. For the comparison versus reslizumab, mepolizumab resulted in lower administration costs (ranging from £113 to £2,533 for mepolizumab and £9,878 for reslizumab) and lower medicine acquisition costs (£109,200 versus £156,400 for mepolizumab and reslizumab respectively) over 10 years.

The ERG noted that the incremental savings associated with mepolizumab were primarily due to lower medicine acquisition costs (Table 13. Scenario analysis undertaken by the ERG which increases the time horizon to 10 years (list price all treatments)). As highlighted in Table 14, when the PAS for mepolizumab was included, incremental savings [redacted] as a result of the [redacted] in mepolizumab medicine acquisition costs.

Table 13. Scenario analysis undertaken by the ERG which increases the time horizon to 10 years (list price all treatments)

Medicines	Acquisition costs	Administration costs	Total costs	Incremental savings vs RSL	Incremental savings vs BRL
MPL 100 mg powder for solution for injection (assumes patients require nurse admin for every dose)	£109,200	£2,533	£111,733	-£44,391*	-
MPL 100 mg solution for injection in pre-filled syringe or pen	£109,200	£1,309	£110,509	-£45,615*	-
MPL 100 mg solution for injection in pre-filled syringe or pen (self-administration)	£109,200	£113	£109,313	-£46,811*	-
RSL 10 mg/mL concentrate for solution for infusion	£146,246	£9,878	£156,124	-	-
BRL 30 mg pre-filled syringe or pen (assumes all patients self-administer) vs MPL 100 mg (assumes patients require nurse admin for every dose)	£130,985	£113	£131,098	-	-£19,365*
BRL 30 mg pre-filled syringe or pen (vs MPL 100mg pre-filled syringe or pen)	£130,985	£716	£131,701	-	-£21,192*
BRL 30 mg pre-filled syringe or pen (self-administration) vs MPL 100mg pre-filled syringe or pen (self-administration)	£130,985	£113	£131,098	-	-£21,785*

Abbreviations: BRL, benralizumab; MPL, mepolizumab; RSL, reslizumab; vs, versus

Notes:

* Denotes incremental savings for mepolizumab

Table 14. Scenario analysis undertaken by the ERG which increases the time horizon to 10 years (including mepolizumab PAS)

Medicines	Acquisition costs	Administration costs	Total costs	Incremental savings vs RSL	Incremental savings vs BRL
MPL 100 mg powder for solution for injection (assumes patients require nurse admin for every dose)	[redacted]	£2,533	[redacted]	[redacted]	-
MPL 100 mg solution for injection in pre-filled syringe or pen	[redacted]	£1,309	[redacted]	[redacted]	-
MPL 100 mg solution for injection in pre-filled syringe or pen (self-administration)	[redacted]	£113	[redacted]	[redacted]	-
RSL 10 mg/mL concentrate for solution for infusion	£146,246	£9,878	£156,124	-	-
BRL 30 mg pre-filled syringe or pen (assumes all patients self-administer) vs MPL 100 mg (assumes patients require nurse admin for every dose)	£130,985	£113	£131,098	-	[redacted]
BRL 30 mg pre-filled syringe or pen (vs MPL 100mg pre-filled syringe or pen)	£130,985	£716	£131,701	-	[redacted]
BRL 30 mg pre-filled syringe or pen (self-administration) vs MPL 100mg pre-filled syringe or pen (self-administration)	£130,985	£113	£131,098	-	[redacted]

Abbreviations: BRL, benralizumab; MPL, mepolizumab; RSL, reslizumab; vs, versus

Notes:

* Denotes incremental savings for mepolizumab

4.1.6.3. OCS use

Due to the lack of comparative data between treatments and some uncertainty surrounding the comparable efficacy of mepolizumab in relation to OCS use, the ERG conducted a scenario analysis which assumed that mepolizumab was less effective than both comparators for OCS reduction. Clinical advice to the ERG noted that patients who do not respond to anti-IL-5 treatments are likely to require treatment with a low dose of OCS indefinitely and will require healthcare costs associated with morbidity/adverse effects. As such, this highly exploratory scenario analysis, uses costs from (Barry et al., 2017[32]) which estimates the cost of systemic steroid induced morbidity associated with severe asthma.

The results outlined in Table 15, assumed that 20% of patients treated with mepolizumab do not respond to treatment and therefore require OCS and associated healthcare costs over a one year period. The ERG estimated the annual OCS cost to be £58, based on a prednisolone 5 mg cost of £1.48 (per pack of 28) and an average patient dose of 15 mg per day. It was assumed that these patients would incur intensive healthcare resource use costs associated with OCS treatment (£4,533), based on a published UK study by Barry et al. (2017).[32]

Based on a list price comparison for all treatments (Table 15), mepolizumab remained cost saving versus both benralizumab and reslizumab despite the assumption that patients receiving mepolizumab will incur additional healthcare resource costs due to OCS consumption. When the PAS for mepolizumab was included, incremental savings versus both comparators were [redacted], due to the [redacted] medicine acquisition costs for mepolizumab (Table 16). It should be reiterated that the ERG consider this analysis to be highly exploratory and likely to result in overestimated costs for mepolizumab.

4.1.6.4. Worst case scenario

An exploratory analysis was conducted to estimate a worst-case scenario for mepolizumab. The analysis in Table 17 has been conducted over a 10-year time horizon and assumes that all mepolizumab doses will be administered by a specialist nurse. Furthermore, the analysis assumes that mepolizumab is the only treatment associated with OCS and healthcare related costs. The ERG note that this analysis is considered highly exploratory and may lack plausibility.

Based on a list price comparison for all treatments (Table 17), mepolizumab remained cost saving versus benralizumab and reslizumab. When the PAS for mepolizumab was included,

incremental savings versus both comparators were [redacted], due to the [redacted] medicine acquisition costs for mepolizumab (Table 18).

4.1.7. Conclusion

Based on list price results for all treatments, mepolizumab resulted in incremental savings versus both benralizumab and reslizumab over a one-year time horizon. When the PAS for mepolizumab is included, incremental savings are [redacted] due to a [redacted] in the medicine acquisition cost for mepolizumab. Scenario analyses conducted by the ERG indicated that results remain robust to changes in key parameters such as an increased time horizon, assuming conservative administration assumptions for mepolizumab and assuming a reduction in mepolizumab efficacy (which is associated with increased OCS use and healthcare costs).

Table 15. Inclusion of OCS related healthcare costs for mepolizumab (list price all treatments)

Medicines	Acquisition costs	Administration costs	Total OCS related costs	Total Costs	Incremental savings vs RSL	Incremental savings vs BRL
MPL 100 mg powder for solution for injection (assumes patients require nurse admin for every dose)	£10,920	£330	£918	£12,168	-£3,521*	-
MPL 100 mg solution for injection in pre-filled syringe or pen	£10,920	£207	£918	£12,045	-£3,643*	-
MPL 100 mg solution for injection in pre-filled syringe or pen (self-administration)	£10,920	£113	£918	£11,951	-£3,738*	-
RSL 10 mg/mL concentrate for solution for infusion	£14,625	£1,064	£0	£15,689	-	-
BRL 30 mg pre-filled syringe or pen (assumes all patients self-administer) vs MPL 100 mg (assumes patients require nurse admin for every dose)	£15,640	£113	£0	£15,753	-	-£3,585*
BRL 30 mg pre-filled syringe or pen (vs MPL 100mg pre-filled syringe or pen)	£15,640	£160	£0	£15,800	-	-£3,755*
BRL 30 mg pre-filled syringe or pen (self-administration) vs MPL 100mg pre-filled syringe or pen (self-administration)	£15,640	£113	£0	£15,753	-	-£3,802*

Abbreviations: BRL, benralizumab; MPL, mepolizumab; OCS, oral corticosteroids; RSL, reslizumab; vs, versus

Notes:

* Denotes incremental savings for MPL

Table 16. Inclusion of OCS related healthcare costs for mepolizumab (including mepolizumab PAS)

Medicines	Acquisition costs	Administration costs	Total OCS related costs	Total Costs	Incremental savings vs RSL	Incremental savings vs BRL
MPL 100 mg powder for solution for injection (assumes patients require nurse admin for every dose)	[redacted]	£330	£918	[redacted]	[redacted]	-
MPL 100 mg solution for injection in pre-filled syringe or pen	[redacted]	£207	£918	[redacted]	[redacted]	-
MPL 100 mg solution for injection in pre-filled syringe or pen (self-administration)	[redacted]	£113	£918	[redacted]	[redacted]	-
RSL 10 mg/mL concentrate for solution for infusion	£14,625	£1,064	£0	£15,689	-	-
BRL 30 mg pre-filled syringe or pen (assumes all patients self-administer) vs MPL 100 mg (assumes patients require nurse admin for every dose)	£15,640	£113	£0	£15,753	-	[redacted]
BRL 30 mg pre-filled syringe or pen (vs MPL 100mg pre-filled syringe or pen)	£15,640	£160	£0	£15,800	-	[redacted]
BRL 30 mg pre-filled syringe or pen (self-administration) vs MPL 100mg pre-filled syringe or pen (self-administration)	£15,640	£113	£0	£15,753	-	[redacted]

Abbreviations: BRL, benralizumab; MPL, mepolizumab; OCS, oral corticosteroids; RSL, reslizumab; vs, versus

Notes:

* Denotes incremental savings for MPL

Table 17. Worst case scenario (list price all treatments)

Medicines	Acquisition costs	Administration costs	Total OCS related costs	Total Costs	Incremental savings vs RSL	Incremental savings vs BRL
MPL 100 mg powder for solution for injection (assumes patients require nurse admin for every dose)	£109,200	£2,533	£9,182	£120,915	-£35,209*	-£10,183*
RSL 10 mg/mL concentrate for solution for infusion	£146,246	£9,878	£0	£156,124	-	-
BRL 30 mg pre-filled syringe or pen (self-administration)	£130,985	£113	£0	£131,098	-	-

Abbreviations: BRL, benralizumab; MPL, mepolizumab; OCS, oral corticosteroids; RSL, reslizumab; vs, versus

Notes:

* Denotes incremental savings for MPL

Table 18. Worst case scenario (including mepolizumab PAS)

Medicines	Acquisition costs	Administration costs	Total OCS related costs	Total Costs	Incremental savings vs RSL	Incremental savings vs BRL
MPL 100 mg powder for solution for injection (assumes patients require nurse admin for every dose)	[redacted]	£2,533	£9,182	[redacted]	[redacted]	[redacted]
RSL 10 mg/mL concentrate for solution for infusion	£146,246	£9,878	£0	£156,124	-	-
BRL 30 mg pre-filled syringe or pen (self-administration)	£130,985	£113	£0	£131,098	-	-

Abbreviations: BRL, benralizumab; MPL, mepolizumab; OCS, oral corticosteroids; RSL, reslizumab; vs, versus

Notes:

* Denotes incremental savings for MPL

5. ERG COMMENTARY ON ROBUSTNESS OF EVIDENCE SUBMITTED

5.1. Summary

The ERG regarded that the clinical evidence presented suggested equal or better effectiveness of mepolizumab on the outcomes presented for a subgroup of patients with blood eosinophil count of ≥400 cells/μl. The ERG also noted that under a range of assumptions relating to administration costs and OCS use and under an assumption of equivalent effectiveness, mepolizumab remained a cost-saving treatment strategy.

5.2. Strengths

The key comparative efficacy data for mepolizumab against benralizumab and reslizumab, was based on a published indirect comparison (ITC) by Busse et al.(2019).[2] Key strengths of the CS include the range and extent of clinical evidence submitted to inform an ITC, including nine RCTs, despite between study variation in respect of length of follow-up, dosing regimens and adminsitration, asthma severity, blood eosinophil counts, and prior exacerbations, most pairwise meta-analyses had low heterogeneity. Studies were of low risk of bias; however, the ERG noted that, for mepolizumab and benralizumab, data were from a subgroup of the ITT population and therefore standard statistical significance thresholds may not apply. Subgroup data for participants with blood eosinophil count ≥400 cells/μl were available for RCTs to inform at least one comparison of mepolizumab against another drug for all outcomes for which meta-analysis was attempted. Key outcomes assessed included exacerbation, exacerbations requiring ED visits/hospitalisation, ACQ scores and FEV_1. Subgroup data for participants with blood eosinophil count ≥400 cells/μl and ≥4 exacerbations in the previous 12 months was available for mepolizumab compared with reslizumab and results were aligned with results from the broader population.

Regarding the cost comparison, the ERG considered that the complexity of the analysis reflected the nature of the decision problem. In addition, given that there may be some uncertainty surrounding what formulation of mepolizumab is likely to be predominantly used in practice and what proportion of patients receiving the pen/syringe will self-administer, it is helpful that the company has provided results for mepolizumab using three different administration assumptions.

5.3. Weaknesses

The ERG considered that the CS lacked clarity in respect of the company's reporting of the identification of studies and presentation of data relevant to the appraisal. The key comparative evidence was from a published ITC (Busse et al., 2019).[2] While the ERG had no substantive issue with this as an approach, it considered that efforts to apply this analysis without appropriate elaboration, expansion or reporting in context of the decision problem in the CS had resulted in a distinct lack of clarity. Despite these deficiencies, the ERG did not regard that substantial additional uncertainty was generated.

While the company presented some data for mepolizumab compared with placebo for the subgroup **blood eosinophil count ≥400 cells /µl and who have had ≥3 exacerbations in the previous 12 months** of interest during clarification, these data were inconsistently available for the comparators, in part due to redaction in previous appraisals. It did, however, present analyses for the broader subgroup of participants with **blood eosinophil count ≥400 cells/µl** from a published ITC (Busse et al., 2019).[2] Based on inclusion criteria from the trials, these participants all had at least one (reslizumab) or two (mepolizumab and benralizumab) severe exacerbations in the previous 12 months. Acknowledging that matching of exacerbation history is of particular importance given effect modification of treatment efficacy by exacerbation history, the ERG regarded that while the broader subgroup was not exactly aligned to the recommendation extension, in principle it was closer than not. While it was not possible to comprehensively assess this in respect of the modification of treatment effect, the ERG considered that it would not substantively alter the conclusion regarding similar or greater effectiveness. In addition, the company also provided data from the published ITC for a more restricted population with a **blood eosinophil count of ≥400 cells/µl and who have had ≥4 exacerbations in the previous 12 months** (mepolizumab vs reslizumab), the results of which were broadly aligned with the broader population. Overall, the ERG considered it to be a reasonable approach, particularly in context of TA565,[1] for which equivalent efficacy for benralizumab compared with reslizumab was based on an assumption.

There were no direct head to head data comparing mepolizumab to reslizumab and benralizumab. As such the assumption of comparable efficacy which underpinned the cost comparison is dependent on an ITC by Busse et al. (2019).[2] Despite some limitations, the ERG regarded that the methods used for the ITC and the interpretation of the results were broadly

appropriate. The ERG further regarded that mepolizumab generally provided similar, if not better, effectiveness as compared to benralizumab and reslizumab within the focal subgroup.

The cost comparison contained several minor discrepancies in relation to unit costs; however, these were subsequently amended by the ERG. Furthermore, the sensitivity analysis provided by the company was considered to be limited. In order to explore further uncertainty, the ERG conducted a number of scenario analyses including a conservative administration analysis for mepolizumab, an analysis using a 10-year time horizon, an analysis which assumed OCS costs for mepolizumab only and a worst-case scenario analysis (which combined all aforementioned analyses).

References

1. Nice. Benralizumab for treating severe eosinophilic asthma. Technology appraisal guidance [TA565]. London: NICE; 2017.
2. Busse W, Chupp G, Nagase H, Albers FC, Doyle S, Shen Q, et al. Anti-IL-5 treatments in patients with severe asthma by blood eosinophil thresholds: Indirect treatment comparison. J Allergy Clin Immunol. 2019;143(1):190-200 e20.
3. European Medicines Agency. Nucala - Marketing Authorisation 2019. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/nucala.
4. GlaxoSmithKline. Paediatric authorisation 2018. Available from: https://www.gsk.com/en-gb/media/press-releases/european-commission-approves-nucala-mepolizumab-for-the-treatment-of-children-with-severe-asthma/.
5. GlaxoSmithKline. Authorisation for self-administration with pre-filled pen or pre-filled syringe 01.08.2019 2019. Available from: https://www.gsk.com/en-gb/media/press-releases/nucala-receives-eu-approval-for-self-administration-by-patients-with-severe-eosinophilic-asthma/.
6. Nice. Mepolizumab for treating severe refractory eosinophilic asthma. Technology appraisal guidance [TA431]. London: NICE; 2017.
7. Nice. Reslizumab for treating severe eosinophilic asthma. Technology appraisal guidance [TA479]. London: NICE; 2017.
8. Lefebvre C GJ, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, Noel-Storr A, Rader T, Shokraneh F, Thomas J, Wieland LS. . Chapter 4: Searching for and selecting studies. . In: Cochrane, editor. Cochrane Handbook for Systematic Reviews of Interventions version 60 (updated July 2019) 2019.
9. Chupp GL, Bradford ES, Albers FC, Bratton DJ, Wang-Jairaj J, Nelsen LM, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. Lancet Respir Med. 2017;5(5):390-400.
10. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014;371(13):1198-207.
11. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet. 2012;380(9842):651-9.
12. Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting beta2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet. 2016;388(10056):2115-27.
13. FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, et al. Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2016;388(10056):2128-41.
14. FitzGerald JM, Bleecker ER, Menzies-Gow A, Zangrilli JG, Hirsch I, Metcalfe P, et al. Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies. Lancet Respir Med. 2018;6(1):51-64.
15. Farne HA, Wilson A, Powell C, Bax L, Milan SJ. Anti-IL5 therapies for asthma. Cochrane Database Syst Rev. 2017;9:CD010834.
16. Bjermer L, Lemiere C, Maspero J, Weiss S, Zangrilli J, Germinaro M. Reslizumab for Inadequately Controlled Asthma With Elevated Blood Eosinophil Levels: A Randomized Phase 3 Study. Chest. 2016;150(4):789-98.

17. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med. 2015;3(5):355-66.
18. Brusselle G, Germinaro M, Weiss S, Zangrilli J. Reslizumab in patients with inadequately controlled late-onset asthma and elevated blood eosinophils. Pulm Pharmacol Ther. 2017;43:39-45.
19. Corren J, Weinstein S, Janka L, Zangrilli J, Garin M. Phase 3 Study of Reslizumab in Patients With Poorly Controlled Asthma: Effects Across a Broad Range of Eosinophil Counts. Chest. 2016;150(4):799-810.
20. Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. Am J Respir Crit Care Med. 2011;184(10):1125-32.
21. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med. 2014;371(13):1189-97.
22. Bourdin A, Husereau D, Molinari N, Golam S, Siddiqui MK, Lindner L, et al. Matching-adjusted comparison of oral corticosteroid reduction in asthma: Systematic review of biologics. Clin Exp Allergy. 2020;50(4):442-52.
23. Bourdin A, Molinari N. Indirect treatment comparison of asthma biologics fraught with methodology issues. J Allergy Clin Immunol. 2019;143(3):1266-7.
24. Gunsoy NB, Bratton DJ, Albers FC, Busse W. Reply. J Allergy Clin Immunol. 2019;143(3):1267-8.
25. Electronic Medicines Compendium. Nucala summary of product characteristics for mepolizumab 2020. Available from: https://www.medicines.org.uk/emc/product/10563/smpc.
26. Khatri S, Moore W, Gibson PG, Leigh R, Bourdin A, Maspero J, et al. Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma. J Allergy Clin Immunol. 2019;143(5):1742-51 e7.
27. Khurana S, Brusselle GG, Bel EH, FitzGerald JM, Masoli M, Korn S, et al. Long-term Safety and Clinical Benefit of Mepolizumab in Patients With the Most Severe Eosinophilic Asthma: The COSMEX Study. Clin Ther. 2019;41(10):2041-56 e5.
28. Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, et al. Oral Glucocorticoid–Sparing Effect of Benralizumab in Severe Asthma. New England Journal of Medicine. 2017;376(25):2448-58.
29. Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, et al. Mepolizumab and Exacerbations of Refractory Eosinophilic Asthma. New England Journal of Medicine. 2009;360(10):973-84.
30. Castro M, Wenzel SE, Bleecker ER, Pizzichini E, Kuna P, Busse WW, et al. Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. Lancet Respir Med. 2014;2(11):879-90.
31. Park HS, Kim MK, Imai N, Nakanishi T, Adachi M, Ohta K, et al. A Phase 2a Study of Benralizumab for Patients with Eosinophilic Asthma in South Korea and Japan. Int Arch Allergy Immunol. 2016;169(3):135-45.
32. Barry LE, Sweeney J, O'Neill C, Price D, Heaney LG. The cost of systemic corticosteroid-induced morbidity in severe asthma: a health economic analysis. Respiratory Research. 2017;18(1):129.

Appendix A: Comparison of PICOS Criteria

	Final scope	SLR	ITC	Busse,2019	Farne Cochrane 2017
Population	People 6 years and older with severe refractory eosinophillic asthma	**People aged ≥12 years** with severe (or refractory/difficult-to-treat/persistent/treatment-resistant/uncontrolled) asthma	**People aged ≥12 years** with severe eosinophilic asthma	**People aged ≥12 years** with severe eosinophilic asthma	Adults and children with a diagnosis of asthma. Focused on collating data from people who had been reported as having eosinophilic asthma to analyse these individuals as a subgroup
Intervention	MPL	Original review: MPL Omalizumab Update review: MPL BRL RSL	**Approved doses or formulations of licensed anti-IL-5 pathway-directed treatments (MPL 100 mg administered SC Q4W**, RSL 3 mg/kg Q4W, BRL 30 mg Q8W [3 × 4 weekly doses followed by Q8W dosing]) compared with PBO only	**Approved doses or formulations of licensed anti-IL-5 pathway-directed treatments** (**MPL 100 mg administered SC every 4 weeks**, RSL 3 mg/kg Q4W, BRL 30 mg every Q8W [3 × Q4W doses followed by Q8W dose]) compared with PBO only	Anti-IL-5 therapy with placebo in addition to current SoC for asthma (ICS +/- second controller such as a LABA), provided treatment period was 16 weeks-plus In the case of dose-ranging studies, we included data only for participants on doses likely to be used clinically, that is, **75 mg IV or 100 mg SC injections of MPL**, 3 mg/kg IV RSL, 20 to 30 mg SC BRL. **For MPL 100 mg SC and RSL IV, these are the licensed doses.** For BRL, used the 30 mg dose used in the 2 Phase 3 studies (Bleecker 2016; FitzGerald 2016), which is likely to be the licensed dose, and included the 20 mg dose in the 3 previous Phase 2a dose-ranging studies (Castro 2015a; Castro 2015b; Park 2016).
Comparator	For people with severe asthma for whom biologics are indicated and suitable according to NICE guidance: BRL, RSL For people with severe asthma for whom currently available biologics are not indicated and suitable: optimized standard therapy without biologics	Specified interventions compared with each other PBO			
Outcome	**Exacerbations (incidence of clinically significant exacerbations including those which require unscheduled contact with healthcare professionals or hospitalization)**	**Exacerbations** **Lung function** **Asthma control** Symptoms **Hospitalisations**	**Clinically significant exacerbations*** **Exacerbations requiring an ED visit/hospitalization** **ACQ score any version**	**Clinically significant exacerbations*** **Exacerbations requiring an ED visit/hospitalization** **ACQ score any version**	**Clinically significant exacerbations*** **Exacerbations requiring an ED visit/hospitalization** **HRQoL (ACQ, AQLQ, SGRQ)**

	Final scope	SLR	ITC	Busse,2019	Farne Cochrane 2017
	Asthma control Use of OCS Patient and clinical evaluation of response **Lung function** Mortality Time to discontinuation Adverse effects of treatment HRQoL		**Change from baseline pre-bronchodilator FEV_1** Note *Defined as an exacerbation requiring treatment with OCS/systemic corticosteroids (for patients on maintenance OCS, a >2-fold increase in dose was required) or requiring an ED visit or hospitalisation	**Change from baseline pre-bronchodilator FEV_1** Note *Defined as an exacerbation requiring treatment with OCS/systemic corticosteroids (for patients on maintenance OCS, a >2-fold increase in dose was required) or requiring an ED visit or hospitalisation	**Measures of lung function FEV_1** **Serious adverse events** **'Clinically significant' adverse events, as defined by those that prompted discontinuation of the intervention and withdrawal from the study** **Eosinophil counts in peripheral blood** Note *Defined as an exacerbation requiring treatment with OCS/systemic corticosteroids (for patients on maintenance OCS, a >2-fold increase in dose was required) or requiring an ED visit or hospitalisation
Study Design	-	RCT	RCT (no restrictions on study timeframe or duration)	RCT (no restrictions on study timeframe or duration)	RCT
Other	-	-	-	-	All (full text, abstract, unpublished)

Abbreviations: ACQ, asthma control questionnaire; AQLQ< asthma quality of life questionnaire; BRL, benalizumab; ED, emergency department; FEV_1, forced expiratory volume in one second; HRQoL, health-related quality of life; ICS, inhaled corticosteroids; IL, interleukin; IV, intravenous; LABA, long-acting beta agonist; MPL, mepolizumab; NICE, National Institute for Health and Care Excellence; OCS, oral corticosteroid; PBO, placebo; PICOS, population, intervention, comparator, outcomes, study design; Q4W, every 4 weeks; Q8W, every 8 weeks; RCT, randomized controlled trial; RSL, reslizumab; SC, subcutaneous; SGRQ, St George's respiratory questionnaire; SoC, standard of care

Appendix B: Evidence Summary

Table 19: Evidence summary

					Inclusion criteria		
Author, year	Tx duration (weeks)	Intervention	N	Drug dose	Blood eosinophil count threshold	Asthma exacerbation	Inhaler use
MPL vs PBO							
Chupp, 2017[9] (MUSCA)	24	**MPL**	274	**100 mg SC Q4W**	≥150 cells/µl (screening); ≥300 cells/µl (previous 12 mths before screening)	≥2 in last yr	High dose ICS +/- other controller drug
		PBO	277	100 mg SC Q4W			
Ortega, 2014[10] (MENSA)	32	**MPL**	194	**100 mg SC Q4W**	≥150 cells/µl (screening); ≥300 cells/µl (previous 12 mths before screening)	≥2 in last yr	High dose ICS +/- other controller drug
		MPL	191	75 mg IV Q4W			
		PBO	191	100 mg SC Q4W			
Bel, 2014[21] (SIRIUS)	32	**MPL**	69	**100 mg SC Q4W**	≥150 cells/µl (screening); ≥300 cells/µl (previous 12 mths before screening)	NA	High dose ICS +/- maintenance OCS + other controller drug
		PBO	66	100 mg SC Q4W			
Pavord,2012[11] (DREAM)	S	MPL	154	75 mg IV Q4W	≥300 cells/µl (previous 12 mths before screening	≥2 in last yr	High dose ICS +/- maintenance OCS + other controller drug
		MPL	152	250 mg IV Q4W			
		MPL	156	750 mg IV Q4W			
		PBO	155	-			
RSL vs PBO							
Bjermer 2016[16] (Study 3081)	24	RSL	104	0.3 mg/kg IV	**≥400 cells/µl (screening)**	≥1 in last yr	Medium dose ICS +/- controller drug
		RSL	106	**3.0 mg/kg IV**			
		PBO	105	-			
Castro 2011[20] (NCT00587288)	12	**RSL**	53	**3.0 mg/kg IV**	Unclear	≥1 in last yr	Medium dose ICS +/- controller drug
		PBO	53	--			

					Inclusion criteria		
Castro 2015[17] (Study 3082/3083)[b]	52	**RSL**	245	**3.0 mg/kg IV**	**≥400 cells/µl (screening)**	≥1 in last yr	Medium dose ICS +/- controller drug incl OCS
		PBO	244	-			
		RSL	232	**3.0 mg/kg IV**			
		PBO	232	-			
Corren 2016[19] (Study 3084)	16	**RSL**	398	**3.0 mg/kg IV**	None **(includes pre-planned subgroup analysis ≥400 cells/µl)**	≥1 in last yr	Medium dose ICS +/- other drug
		PBO	98	-			
BRL vs PBO							
Bleecker, 2016[12] (SIROCCO)[c]	48	**BRL**	267	**30 mg SC Q8W**	≥300 cells/µl	≥2 in last yr	High dose ICS LABA +/- maintenance OCS + other controller drug
		BRL	275	30 mg SC Q4W			
		PBO	267	30 mg SC Q8W			
Fitzgerald, 2016[13] (CALIMA)[c]	56	**BRL**	239	**30 mg SC Q8W**	≥300 cells/µl	≥2 in last yr	High dose ICS LABA +/- maintenance OCS + other controller drug
		BRL	241	30 mg SC Q4W			
		PBO	248	30 mg SC Q8W			

Abbreviations: BRL, benralizumab; Ex, exacerbation; FEV^1, forced expiratory volume in one second; ICS, inhaled corticosteroids; IV, intravenous; LABA, long-acting beta-agonist; MPL, mepolizumab; mths, months; OCS, oral corticosteroids; PBO, placebo; Q4W, every four weeks; Q8W, every 8 weeks; RSL, reslizumab; SC, subcutaneous; D, standard deviation; Tx, treatment; yr, year

Notes:

Bold **intervention** and **drug dose** approved dose and formulation

[a] Subgroup analysis conducted blood eosinophil count ≥400 cells/µl

[b] Study results for Study 3082/3083 reported in Castro 2015[17] and Brusselle 2017[18]

[c] Study results for SIROCCO (Bleecker 2016[12]) and CALIMA (FitzGerald 2016[13]) also reported in pooled analysis (FitzGerald 2018[14])

Source: MUSCA (Chupp 2017[9]); MENSA (Ortega 2014[10]); SIRIUS (Bel 2014[21]); DREAM (Pavord 2012[11]); CALIMA (FitzGerald 2016[13]); SIROCCO (Bleecker 2016[12]); Study 3081 (Bjermer 2016[16]); Study 3082/3083 (Castro 2015[17]), (Brusselle 2017[18]); Study 3084 (Corren 2016[19]); NCT00587288 (Castro 2011[20])

Appendix C: Baseline eosinophils ≥300 cells/ and ≥4 exacerbations

Table 20. Subgroup baseline characteristics: subgroup ≥300 cells/µL and ≥4 exacerbations needing corticosteroids in the previous 12 months

	MPL 100 mg SC[a]	MPL 100 mg SC / MPG 75 mg[b]	PBO[a]
N (Total ITT)	[redacted]	[redacted]	[redacted]
n (subgroup)	[redacted]	[redacted]	[redacted]
Age years, mean (SD)	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]
BMI kg/m^2, mean (SD)	[redacted]	[redacted]	[redacted]
Total exacerbations			
4, n (%)	[redacted]	[redacted]	[redacted]
≥4, n (%)	[redacted]	[redacted]	[redacted]
Total exacerbations that required ER visits and/or hospitalisation			
0, n (%)	[redacted]	[redacted]	[redacted]
1, n (%)	[redacted]	[redacted]	[redacted]
2, n (%)	[redacted]	[redacted]	[redacted]
3, n (%)	[redacted]	[redacted]	[redacted]
4, n (%)	[redacted]	[redacted]	[redacted]
≥4, n (%)	[redacted]	[redacted]	[redacted]
Total exacerbations that required hospitalisation, n			
0, n (%)	[redacted]	[redacted]	[redacted]
1, n (%)	[redacted]	[redacted]	[redacted]
2, n (%)	[redacted]	[redacted]	[redacted]
3, n (%)	[redacted]	[redacted]	[redacted]
4, n (%)	[redacted]	[redacted]	[redacted]
≥4, n (%)	[redacted]	[redacted]	[redacted]
Duration of asthma, mean (SD)	[redacted]	[redacted]	[redacted]
12 months prior to Visit 1 elevated peripheral blood eosinophil count ≥300			
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
At Visit 1 elevated peripheral blood eosinophil count ≥150 cells/µl[c]			
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]

	MPL 100 mg SC[a]	MPL 100 mg SC / MPG 75 mg[b]	PBO[a]
Maintenance OCS use, n (%)	[redacted]	[redacted]	[redacted]
BL OCS daily dose[d] (prednisolone equivalent), mean (SD)	[redacted]	[redacted]	[redacted]
Baseline Blood eosinophils (Gl/L), Geo mean (Std Logs)	[redacted]	[redacted]	[redacted]

Abbreviations: BMI, body mass index; ER, emergency room; ITT, intention to treat; IV intravenous; MPL, mepolizumab; OCS, oral corticosteroids; PBO, placebo; SC, subcutaneous; SD, standard deviation

Notes:

[a] MUSCA and MENSA studies

[b] MUSCA< MENSA and DREAM studies

[c] Elevated peripheral blood eosinophil count ≥150 cells/µl at Visit 1 determined from laboratory data collected at this visit

[d] Daily dose derived for participants that indicated they were on regular maintenance OCS at baseline

Source: Clarification Response, Table A11.1

Table 21. Clinically significant exacerbations: subgroup ≥300 cells/µL and ≥4 exacerbations needing corticosteroids in the previous 12 months

	MPL 100 mg SC	MPL 100 mg SC / MPL 75 mg IV	PBO
N (Total, ITT)	467	811	624
Subgroup ≥400 cells/µL and ≥3 exacerbations by trial:			
MENSA, n[a]	[redacted]	[redacted]	[redacted]
Exacerbation rate / year	[redacted]	[redacted]	[redacted]
Rate ratio MPL/PBO (95% CI)[b]	[redacted]	[redacted]	[redacted]
MUSCA, n[a]	[redacted]	[redacted]	[redacted]
Exacerbation rate / year	[redacted]	[redacted]	[redacted]
Rate ratio MPL/PBO (95% CI)[b]	[redacted]	[redacted]	[redacted]
DREAM, n[a]	NA	[redacted]	[redacted]
Exacerbation rate / year	NA	[redacted]	[redacted]
Rate ratio MPL/PBO (95% CI)[b]	NA	[redacted]	[redacted]
Meta-analysis (MENSA/MUSCA/DREAM) , n[a]	[redacted]	[redacted]	[redacted]
Rate ratio MPL/PBO (95% CI)[c]	[redacted]	[redacted]	[redacted]

Abbreviations: BMI, body mass index; ER, emergency room; ITT, intention to treat; IV, intravenous; MPL, mepolizumab; OCS, oral corticosteroids; PBO, placebo; SC, subcutaneous; SD, standard deviation

Notes:

[a] Number of subjects with analysable data

[b] Analysis performed using a negative binomial regression model with covariates of treatment group, region, exacerbations in the year prior to the study (as an ordinal variable), baseline OCS (yes, no)) and baseline percent predicted FEV_1 with logarithm of time on treatment as an offset variable

[c] Inverse variance weighed fixed effects meta-analysis

Source: Clarification Response Table A11.2: MUSCA (Chupp 2017[9]); MENSA (Ortega 2014[10]); DREAM (Pavord, 2012[11])

Table 22. Clinically significant exacerbations: Subgroup analysis of clinically significant exacerbations: subgroup ≥300 cells/µL and ≥4 exacerbations needing corticosteroids in the previous 12 months

Comparison	≥4 exacerbations in prior year RR (95% CI)
MPL vs PBO	0.23 (0.14, 0.37)
BRL vs PBO	0.46 (0.31, 0.68)
MPL vs BRL	0.50 (0.27, 0.94)

Abbreviations: BRL, benralizumab; CI, confidence interval; MPL, mepolizumab; RR, risk ratio; RSL, reslizumab; vs, versus

Source: Clarification Response A11 Table E10: Busse et al., 2019[2]

Appendix D: Baseline eosinophils ≥400 cells/µL and ≥4 exacerbations

During clarification (clarification question A11), the company also provided results comparing mepolizumab and reslizumab for a more restricted subgroup comprising patients with a blood eosinophil count of ≥400 cells/µl and who have had ≥4 severe asthma exacerbations in the previous 12 months. The results from this analysis were extracted from the additional results section of the published ITC (Busse et al., 2019[2]).

Table 23. Clinically significant exacerbations: subgroup analysis on the rate of clinically significant exacerbations: subgroup ≥400 cells/µL and ≥4 exacerbations needing corticosteroids in the previous 12 months

Comparison	≥4 exacerbations in prior year RR (95% CI)
MPL 100 mg SC vs PBO	0.14 (0.07, 0.29); p<0.001
RSL 3 mg/kg vs PBO	0.36 (0.22, 0.58); p<0.001
MPL 100 mg SC vs RSL 3 mg/kg	0.40 (0.17, 0.93); p<0.05

Abbreviations: CI, confidence interval; MPL, mepolizumab; PBO, placebo; RR, risk ratio; RSL, reslizumab; SC, subcutaneous; vs, versus

Source: Clarification Response A11 Table E10: Busse et al., 2019[2]

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

Review of NICE Technology Appraisal Guidance TA431: mepolizumab for treating severe eosinophilic asthma ID3750

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm on Thursday 6 August 2020** 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.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Interpretation of proposed new Sub-population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 10 Section 1.2 The use of AND in this sentence could imply a more restrictive sub-population, please replace "AND" with "OR" "The rationale for this focus was to align the recommendation for mepolizumab with that of benralizumab i.e. baseline eosinophil count of ≥300 cells/µl **and** who have had ≥4 *exacerbations in the previous 12 months* ***and*** *baseline eosinophil count of ≥400 cells*/µl and who have had ≥3 exacerbations in the previous 12 months."	"The rationale for this focus was to align the recommendation for mepolizumab with that of benralizumab i.e. baseline eosinophil count of ≥300 cells/µl and who have had ≥4 exacerbations in the previous 12 months **OR** baseline eosinophil count of ≥400 cells/µl and who have had ≥3 exacerbations in the previous 12 months."	To provide clarity on the two different eligible sub-populations	The report has been edited to clarify that either baseline eosinophil count of ≥300 cells/µl and who have had ≥4 exacerbations in the previous 12 months or baseline eosinophil count of ≥400 cells/µl and who have had ≥3 exacerbations in the previous 12 months. See edit Section 1.2, p10

Issue 2 Inaccurate reference to Sub-population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 12, 2nd Para. The wrong sub-population is being referred to in this sentence: *"While the company presented some data for the specific*	The text should read: *"While the company presented some data for the specific subgroup of interest (baseline eosinophil count ≥400 cells/µl and* ***≥3*** *exacerbations), …"*	To clarify correct sub-population being referred to	The report has been corrected. See edit p12, second paragraph

*subgroup of interest (baseline eosinophil count ≥400 cells/µl and **≥4** exacerbations)…"*			

Issue 3 Inaccurate reference to Sub-population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 15, 1st Para, text in bold. The wrong sub-population is being referred to in this sentence: "*In addition, the company also provided data from the published ITC for a more restricted population with a blood eosinophil count of ≥400 cells/µl and who have had **≥3** exacerbations in the previous 12 months (mepolizumab vs reslizumab),…"*	The text should read: *"In addition, the company also provided data from the published ITC for a more restricted population with a blood eosinophil count of ≥400 cells/µl and who have had ≥4 exacerbations in the previous 12 months (mepolizumab vs reslizumab),…"*	To clarify correct sub-population being referred to	The report has been corrected. See edit p15, first paragraph

Issue 4 Inaccurate interpretation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 27, final sentence *"The ERG noted inconsistency between the results reported for*	Suggest removal of this sentence as does not accurately reflect the analyses conducted.	We do not agree with this sentence, specifically that there are inconsistencies with the results	Thank you for your comment. The ERG has revised the text to clarify.

reduction in exacerbation rate for the subgroup with eosinophil count ≥300 cells per microlitre and ≥3 exacerbation using the 100 mg dose in the ITC, and the new meta-analysis for the same dose provided by the company (Tables E10 & Table A11.2, respectively).”		presented in the submission compared with those presented in the ITC. The criteria to select the two sub-populations for analysis differ e.g. in the ITC, there was an additional criterion of patients having to have an ACQ score of ≥1.5 at baseline and also the IV formulation was excluded.	See edit p27

Issue 5 Inaccurate reporting of results in Table 5

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>Table 5

The p-values quoted for some of the Busse et al ITC analyses are incorrect.

Also, as the comparison between benralizumab and reslizumab has been reversed</td>
<td>The highlighted p-values are the correct values now and Table 5 should be updated.
The highlighted 95%CI values are incorrect as the comparison has been reversed, so this CI is no longer valid and need to be re-calculated
<table>
<tr><th></th><th>MPL vs BRL</th><th>MPL vs RSL</th><th>BRL vs RSL</th></tr>
<tr><td>Rate of clinically significant exacerbations</td><td>MPL reduces the rate significantly (RR 0.55, 95% CI [0.35, 0.87]; p=0.011)</td><td>MPL reduces the rate significantly (RR 0.55, 95% CI [0.36, 0.85]; p=0.007)</td><td>No difference (RR 1.00, 95% CI [0.71, 1.40])</td></tr>
</table>
The highlighted CI below is the wrong way around and should it read [-0.23, 0.15] as the comparison has been reversed
<table>
<tr><th></th><th>MPL vs BRL</th><th>MPL vs RSL</th><th>BRL vs RSL</th></tr>
<tr><td>Patient-reported asthma control (ACQ score)</td><td>MPL has greater improvement from baseline (difference: –0.36 95% CI [–0.66, –0.05]; p=0.023)</td><td>MPL has greater improvement from baseline (difference: –0.39 95% CI [–0.66, –0.12]; p=0.004)</td><td>BRL is not significantly better (difference: -0.04, 95% CI [-0.15, 0.23])</td></tr>
</table>
</td>
<td>Incorrect or missing results presented</td>
<td>The p values have been checked vs the CS/publication and corrected as indicated by the company. The comparison RSL vs BRL has been aligned with the analysis conducted by Busse et al., 2019 and as</td>
</tr>
</table>

<table>
<tr>
<td>compared to what was done in the ITC, this affects some of the results presented</td>
<td>The highlighted p-value was missed off the table
<table>
<tr><th></th><th>MPL vs BRL</th><th>MPL vs RSL</th><th>BRL vs RSL</th></tr>
<tr><td>Change from baseline in pre-bronchodilator FEV_1</td><td>MPL is not significantly worse (difference: -0.05, 95% CI [-0.18, 0.09])</td><td>MPL is not significantly better (difference: 0.06, 95% CI [-0.05, 0.17])</td><td>BRL is more effective (difference: 0.11, 95% CI [0.01, 0.20]), p=0.025</td></tr>
</table>
</td>
<td></td>
<td>reported in the CS, i.e. RSL vs BRL not BRL vs RSL.
See edit Table 5, p29</td>
</tr>
</table>

Issue 6 Misrepresentation of ITC results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 36, final paragraph, the sentence below does not accurately reflect the ITC results. *"Based on the ITC mepolizumab appeared to demonstrate comparable efficacy versus both comparators, albeit benralizumab and reslizumab were considered superior for several outcomes (see Table 5 and Table 6 in Section 3.3.3)."*	Propose the sentence is modified to: *"Based on the ITC, mepolizumab appeared to demonstrate superior efficacy versus both comparators for clinically significant exacerbations and asthma control, however benralizumab was considered superior to mepolizumab for change from baseline in pre-bronchodilator FEV1 (see Table 5 and Table 6 in Section 3.3.3)."*	More accurately reflect the results seen in the ITC	The inclusion of additional study detail seems reasonable. The company's suggested edits have been incorporated. See edit Sn 4.1.1, pg36

Issue 7 Interpretation of resource costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 38, last bullet point, 2nd sentence: "Administration costs were estimated to be **£113 per year**, which included monitoring and administration costs for the first three initial doses only".	As written it reads as if admin costs were £113 every year, however it is only for the first year for the patient when the medicine is administered by a nurse for the first 3 doses. thereafter, the patients will self-administer all doses each year so there is no administration cost. Suggest re-wording to: "Administration costs were estimated to be £113 for the first year, which included monitoring and administration costs for the first three initial doses only, and then there are no administration costs, thereafter".	To accurately reflect the admin costs	The text has been revised as follows to clarify that the administration cost was £113, applicable only in the first year. However, the ERG had noted that these were administration costs for the first three doses. See edit, Sn 4.1.3, p38

Issue 8 Drug acquisition costs and administration for benralizumab

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 13 Although the 10-year analysis was conducted by the ERG and not by GSK, we think that the drug acquisition costs and administration for benralizumab may have been over-estimated as it appears to be based on the use of 8 doses per year. The dosing schedule for benralizumab results	Calculations to be re-done for benralizumab	Incorrect estimation of Year 2+ costs for benralizumab	Thank you for your comment. The ERG has re-estimated benralizumab costs (in the 10-year analyses), from Year 2 onwards to reflect the correct dosing. See edit, p42 and Tables 13, 14, 17 and 18 (p 43, 44, 49 and 49 respectively)

in the use of 6 doses in year 2 and 7 doses in year 3. Subsequent years would continue on the 6 and 7 dose schedule for alternate years through to the end of the 10 year time horizon.			

Issue 9 Inaccurate interpretation of OCS outcome evidence

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 45, Section 4.1.6.3, 1st para We believe the following sentence is inaccurate *"There are published clinical studies which suggest that mepolizumab may not be as effective as benralizumab with respect to reduction in OCS use (Barry et al., 2017)."*	We proposed this sentence is removed or re-written to provide a better reflection of the available evidence.	There is no robust clinical evidence that indicates a true difference in OCS reduction effectiveness between mepolizumab and reslizumab. The trials SIRIUS and ZONDA provide comparable results with this endpoint. In addition, we do not believe that Barry et al, 2017 is an appropriate reference as it is a study discussing the cost of systemic steroid morbidity.	The sentence has been re-worded to reflect the lack of comparative efficacy data between treatments with regards to OCS reduction. See edit Sn 4.1.6.3, p45, 1st paragraph The ERG considers Barry et al to be a relevant and appropriate source. Based on clinical expert input to the ERG, patients who do not respond to mepolizumab or other anti-IL-5 treatments will remain on a low dose of OCS indefinitely AND will also incur healthcare resource costs (accounting for morbidity and adverse events associated with systemic OCS use). The study is relatively recent and costs are estimated in GBP.

Issue 10 Calculation of impact of mepolizumab non-responders on OCS use

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 45, Section 4.1.6.3, 2nd para We believe the following sentence is inaccurate *The results outlined in Table 15, assumed that 20% of patients treated with mepolizumab do not respond to treatment and therefore require continuous OCS use.*	We propose that the OCS analysis is reconsidered in terms of cost incurred with mepolizumab non-responders.	If a patient on mepolizumab does not respond to treatment, they would discontinue treatment by the end of Year 1. Therefore, OCS costs should not be applied to mepolizumab beyond the time of discontinuation.	Thank you for your comment. Table 15 provides a one-year snap shot of OCS related healthcare costs, assuming that 20% of patients on mepolizumab do not respond to treatment over this time period. No OCS related costs are applied to the mepolizumab arm beyond one year. The report has been updated to state that this analysis is conducted over one year. See edit Sn 4.1.6.3, p45, 2nd paragraph As outlined in response to Issue 9, based on clinical expert input to the ERG, non-responders are assumed to require OCS treatment and associated healthcare resource use (accounting for morbidity and adverse events associated with systemic OCS use). It is worth noting that the ERG consider the OCS analysis to be highly exploratory and this has been highlighted in the report.

Issue 11 Inaccurate reference to Sub-population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 51, Section 5.3, 2nd Para. The wrong sub-population is being referred to in this sentence: While the company presented some data for the specific subgroup of interest (baseline eosinophil count ≥400 cells/μl and **≥4** exacerbations in the previous 12 months)…"	The text should read: *"While the company presented some data for the specific subgroup blood eosinophil count ≥400 cells/μl and who have had* ***≥3*** *exacerbations in the previous 12 months), …"*	To clarify correct sub-population being referred to	This has been corrected. See Sn 5.3, p51

CIC:

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 12, Title for Section 1.6. Please could you mark up the word "lower" in the title as CIC	Assuming this refers to the confidential PAS analysis conducted by ERG as well as the comparison GSK did vs the list price of comparators	Commercial in confidence. May provide comparator manufacturers an idea on the level of PAS discount	The heading has been changed to avoid the inclusion of results information, as follows "Cost comparison approach was applicable" See edit Sn 1.6, p12

Typographical errors:

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 11, last sentence Typo of “administration” Page 39, Section 4.1.4, end of last sentence Typo of “continuous”	Correct typo	N/A	Thank you. These typographical errors have been corrected. See Sn 1.5, p11 and Sn 4.1.4, p39