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

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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.

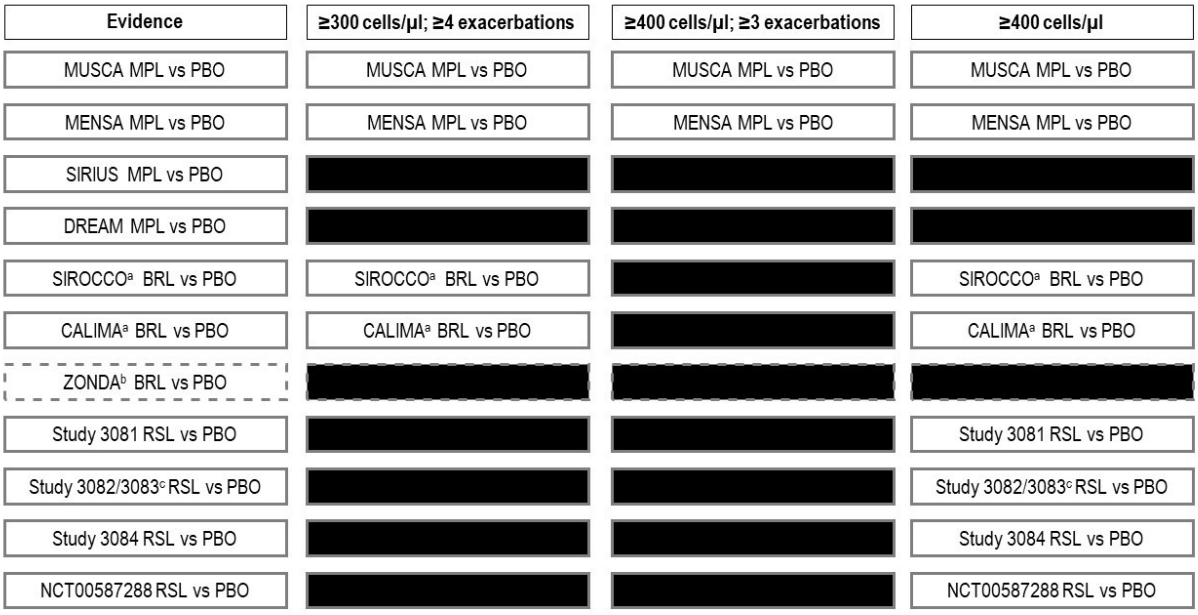
(2019)[2] (Section 3.2.3), and positioned this ITC as the key comparative efficacy data for mepolizumab versus benralizumab and reslizumab. The ITC compared the efficacy of mepolizumab, reslizumab and benralizumab at the approved doses (per summary of product characteristics [SmPC]), for people with 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).

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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 (GI/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]