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Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Reslizumab for treating asthma with elevated blood eosinophils inadequately controlled by inhaled corticosteroids

Produced by Southampton Health Technology Assessments Centre

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LIST OF ABBREVIATIONS

AAAI	American Academy of Allergy, Asthma and Immunology
ACQ	Asthma Control Questionnaire
AE	Adverse event
AiC	Academic in confidence
AQLQ	Asthma Quality of Life Questionnaire
ATS	American Thoracic Society
BMI	Body mass index
BSC	Best standard of care
BTS	British Thoracic Society
CHEST	American College of Chest Physicians
CHMP	Committee for Medicinal Products for Human Use
CiC	Commercial in confidence
CI	Confidence interval
EAACI	European Academy of Allergy and Clinical Immunology
EMA	European Medicines Agency
ERS	European Respiratory Society
FAS	Full analysis set
FDA	US Food and Drug Administration
FEF	Forced expiratory flow
$FEF_{25–75\%}$	Forced expiratory flow at 25–75% forced vital capacity
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
HRQoL	Health-related quality of life
HTA	Health technology assessments
ICER	Incremental cost-effectiveness ratio
ICS	Inhaled corticosteroid
IgE	Immunoglobulin E
IL-5	Interleukin-5
ISAF	International Severe Asthma Forum
ITT	Intention-to-treat

LABA	Long-acting beta-agonist
LTRA	Leukotriene receptor antagonist
OCS	Oral corticosteroid
PAS	Patient access scheme
PASLU	Patient Access Schemes Liaison Unit
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
SABA	Short-acting beta-agonist
SAE	Serious adverse event
SAS	Safety analysis set
SD	Standard deviation
SE	Standard error
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SGRP	St George's Respiratory Questionnaire

SUMMARY

Scope of the company submission

The company's submission (CS) generally reflects the scope of the appraisal issued by the National Institute for Health and Care Excellence (NICE). The scope considers adults with asthma with elevated blood eosinophils inadequately controlled by inhaled corticosteroids. The scope does not define elevated blood eosinophils. The company included patients with ≥400 eosinophils per μL which clinical experts advising the ERG agreed is reasonable. The company's pivotal clinical trials of effectiveness evidence included people aged from 12 years upwards; however, as the mean age in the trials exceeded 40 years the trial populations do not appear to conflict with the scope (for specific analyses in the economic model the company utilised an adults-only subgroup and individual patient data from the trials). The NICE scope does not specify patients' exacerbation history, but the company's economic analysis requires that patients should have had a specified number of asthma exacerbations in the preceding 12 months. The intervention (reslizumab), comparators (omalizumab and best standard of care; BSC), and the outcomes assessed by the company are consistent with the NICE scope. A key assumption is made by the company that placebo in trials of both reslizumab and omalizumab is equivalent to BSC.

Summary of submitted clinical effectiveness evidence

The company conducted a systematic review to identify randomised controlled trials (RCTs) of reslizumab and omalizumab. Overall, the literature searches for clinical effectiveness evidence conducted by the company were appropriate, although searches were five months out of date. The ERG did not identify any additional potentially relevant studies of reslizumab but we did identify one potentially relevant study of omalizumab, which had been published since the date of the company's search. The company's searches identified five RCTs of reslisumab versus placebo and 16 RCTs of omalizumab versus various comparators, which were primarily placebo or BSC. The company stated that one of the reslizumab trials (Res-5-0010) was excluded from further consideration and the CS does not report any demographic details or quality assessment for this trial. However, the company subsequently included this trial in a number of outcome analyses.

The CS presents clinical effectiveness evidence in three main sections: results of the relevant clinical trials of reslizumab versus placebo; a direct comparison meta-analysis of the results of

these trials; and an indirect treatment comparison (ITC) comparing reslizumab against omalizumab via the common comparator of placebo. In practice, the comparator in the omalizumab trials was not always placebo but sometimes described as BSC, optimised asthma therapy, or a control group, but the CS does not discuss this and assumes all comparators were equivalent to BSC.

Characteristics of the reslizumab trials

Two of the reslizumab trials (referred to as 3082 and 3083) were identical, 52-week trials, with clinically significant exacerbation rates as their primary outcome. These trials randomised 489 and 464 patients respectively and are referred to *in this report* as the company's pivotal trials. The remaining trials had durations of 16 weeks (trials 3081, 3084) or 15 weeks (trial Res-5-0010) and randomised totals of 106 patients (Res-5-0010), 315 patients (trial 3081) and 496 patients (trial 3084). In each trial the intervention group received 3.0 mg/kg reslizumab administered every 4 weeks in accordance with the summary of product characteristics (SmPC). Trials 3081, 3084 and Res-5-0010 differed slightly in their inclusion criteria compared to the pivotal clinical trials; in particular, unlike the other trials, trial 3084 did not require patients to have ≥400 eosinophils per μL at baseline. The primary outcomes were changes in FEV1 (trials 3081, 3084) and changes in asthma control assessed using ACQ scores (Res-5-0010). The five reslizumab trials were all double-blind and all were sponsored by the company or (Res-5-0010) by one of its subsidiaries.

Outcomes

The company analysed seven outcomes which are relevant to the NICE scope: asthma control, based on Asthma Control Questionnaire (ACQ) scores; rates of clinically significant exacerbations; the proportion of patients hospitalised due to exacerbations; lung function (forced expiratory volume in 1 second: FEV1); discontinuations due to adverse events; frequency of serious adverse events; and health-related quality of life (HRQoL), assessed using Asthma Quality of Life Questionnaire (AQLQ) scores. Asthma control, lung function and HRQoL were analysed as changes from baseline to 16 and/or 52 weeks (depending upon data availability) whilst exacerbation rates were standardised to person-years to account for trial differences in assessment times. These seven outcomes were analysed both in the direct comparison meta-analysis of reslizumab versus placebo and the indirect treatment comparison

of reslizumab versus omalizumab. The company used a standard frequentist approach to analyse all outcomes except exacerbations, which were modelled using a Bayesian approach. We consider this to be reasonable, as the frequentist approach offers simplicity and transparency whilst the exacerbation rate data are well suited to Bayesian analysis.

The CS presents some further outcomes which are relevant to the NICE scope but which were not meta-analysed by the company: lung function (% predicted FEV1, FVC, $FEF_{25-75\%}$); and HRQoL (Asthma Symptom Utility Index; ASUI). The CS also presents two additional outcomes which are not specified in the NICE scope: changes in short-acting beta agonist (SABA) use and blood eosinophil counts. These outcomes are presented and discussed in the current report as supporting information.

Results of the direct comparison meta-analysis of reslizumab versus placebo

Improvement in asthma control at 16±1 weeks (5 trials), indicated by a decrease in ACQ score, occurred in both reslizumab and placebo groups. The difference in the mean change was statistically significantly larger in patients randomised to reslizumab than those randomised to placebo, and both fixed-effects and random-effects models gave the same result (mean difference –0.24; 95% CI –0.32 to –0.17). All patients in both groups had scores >2 at baseline indicating poorly controlled asthma, but the CS does not discuss whether the observed changes in ACQ scores would have altered this classification. Insufficient data were available to meta-analyse ACQ scores at 52 weeks.

The rate of clinically significant exacerbations, standardised to person-years (3 trials), was statistically significantly lower in the reslizumab group than the placebo group with a fixed-effects model (hazard ratio 0.44; 95% credible interval 0.35 to 0.56) but not with a random-effects model (0.43; 95% credible interval 0.17 to 1.10). Fixed and random effects models for the rate of exacerbations indicated that the Bayesian analysis probability of reslizumab performing better than placebo was 100% and 97%, respectively.

For the proportion of patients hospitalised due to exacerbations up to 52 weeks (2 trials), both fixed-effects and random-effects models gave identical results, showing no significant difference between the reslizumab and placebo groups (odds ratio 0.73; 95% CI 0.36 to 1.47); however, hospitalisation events were rare in the trials.

Improvement in lung function, indicated by the change in FEV1, was statistically significantly larger in the reslizumab group than the placebo group at both 16±1 weeks (5 trials; random-effects mean difference 0.13 L; 95% CI 0.07 to 0.18) and 52 weeks (2 trials; random-effects mean difference 0.13 L (0.08; 0.18). Fixed-effects and random-effects models gave similar or identical results at each time point.

For discontinuations due to adverse events ~~(3 trials)~~ the fixed and random effects models gave identical results, which showed no statistically significant differences between reslizumab and placebo treated patients at either 16±1 weeks (3 trials; odds ratio 0.83; 95% CI 0.17 to 4.16) or 52 weeks (2 trials; odds ratio 0.70; 95% CI 0.33 to 1.5).

For serious adverse events ~~up to 52 weeks (2 trials)~~ the fixed and random effects models gave identical results, and these showed no statistically significant differences between the reslizumab and placebo groups at 16±1 weeks (3 trials; odds ratio 0.82; 95% CI 0.43 to 1.55) and at 52 weeks (2 trials; odds ratio 0.71; 95% CI 0.47 to 1.08). ~~Insufficient data were available for analysis at 16 weeks~~.

For HRQoL, fixed and random-effects models for the change in AQLQ score gave identical results. The mean difference in change from baseline at 16 weeks (3 trials) was 0.24 (95% CI 0.12 to 0.36) whilst the mean difference at 52 weeks (2 trials) was 0.33 (95% CI 0.19 to 0.46), indicating at both timepoints that the improvement in AQLQ score in the reslizumab group was statistically significantly larger than in the placebo group.

Whilst the individual trials contributing to the direct comparison meta-analysis were generally well conducted and (except Res-5-0010) well reported in the CS, the ERG has concerns about the sample sizes used in the analyses which for all efficacy outcomes were smaller than the number randomised in each trial and (where defined) also smaller than the 'full analysis set'. The missing data are not explained in the CS and are particularly problematic for trials 3081 and 3084, where, according to sample sizes reported in the CS, up to 20% of the number randomised was missing in trial 3081 and up to 15.3% in trial 3084. In general, the missing data in the pivotal trials 3082 and 3083 were less than 2% of the number randomised, except for the analysis of FEV1 where 7.8% of the number randomised was missing in trial 3083, and the

analysis of AQLQ where up to 6.9% of the number randomised was missing in trial 3082 and up to 8.2% in trial 3083.

Results of the trials included in the CS show that for the asthma control, lung function and HRQoL outcomes, improvements from baseline occurred in the placebo group as well as in the reslizumab group, suggestive of a placebo effect. This is not unexpected, as placebo effects are well-known in trials of asthma medications. However, the company does not discuss whether this has any implications for their assumption that BSC and placebo are equivalent.

Results of the indirect treatment comparison of reslizumab versus omalizumab

The company's indirect treatment comparison (ITC) is based on an assumption that effects of omalizumab are comparable in patients irrespective of their blood eosinophil levels. This assumption is necessary because only patients in the reslizumab trials had elevated blood eosinophil levels.

The ITC is based on a simple network, comprising only trials of reslizumab versus placebo (maximum 5) and trials of omalizumab versus placebo or BSC (maximum 16). In practice, the company included some omalizumab trials which referred to optimised asthma therapy or a control group as their comparator rather than BSC, but the ITC Report provided by the company does not mention or discuss this. Although in theory 16 omalizumab trials were potentially available for the ITC, the maximum number included for any given outcome, was four, reflecting that most of the omalizumab trials did not report all of the outcomes of interest. The analytical approach for the ITC was similar to that for the direct comparison meta-analysis (which, as noted above, we consider reasonable): exacerbation rates were analysed with a Bayesian approach and all other outcomes were analysed with a frequentist approach.

The ITC results for change in asthma control at 16±1 weeks are based on five reslizumab and two omalizumab trials. One of the omalizumab trials was open-label and the company conducted a sensitivity analysis excluding this trial (i.e. leaving only one omalizumab trial in the analysis). When both omalizumab trials were included in the ITC, the mean difference in the change in ACQ score at 16 weeks for reslizumab compared to omalizumab was 0.30 (95% CI 0.10 to 0.55) with a fixed-effects model and 0.15 (95% CI –0.31 to 0.61) with a random-effects

model. Excluding the open-label omalizumab trial gave a fixed-effects mean difference of –0.24 (95% CI –0.68 to 0.19). The company concluded that, based on the random-effects model, reslizumab is comparable to omalizumab in terms of change from baseline in ACQ score at 16±1 weeks. Insufficient data were available for analysis at 52 weeks.

ITC results for rates of clinically significant exacerbations, standardised to person-years, are based on three reslizumab and three omalizumab trials. The company used the deviance information criterion (DIC), which was marginally smaller for fixed-effects than the random-effects model (78.06 versus 78.81), to justify ~~*presenting only*~~ *prioritising* results of a fixed-effects analysis for this outcome *(random-effects results are presented separately in ITC Report Appendix 12)*. The ERG disagrees with this approach, because such a small difference in the DIC is not informative, and also because a random-effects model is arguably more plausible. As one of the omalizumab trials was open-label, the company conducted a sensitivity analysis omitting this trial. The fixed-effects ITC hazard ratio favoured reslizumab over omalizumab in terms of having a lower rate of clinically significant exacerbations (0.80; 95% CI 0.44 to 1.44) and this effect was strengthened in the sensitivity analysis limited to double-blind studies (0.54; 95% CI 0.26 to 1.12). The Bayesian probability that reslizumab will perform better than omalizumab was 77% in the full analysis and 95% in the analysis limited to double-blinded trials. *However, in the random-effects analysis (which included the open-label trial) the median hazard ratio comparing reslizumab against omalizumab for clinically significant exacerbations was considerably smaller (0.18; 95% CrI 0.18 to 2.82).* ~~*However, the robustness of these results is unclear given that no random-effects analysis is available for comparison.*~~

The ITC analysis of patients hospitalised due to exacerbations could only be conducted for 52 weeks due to a lack of data at 16 weeks. Two reslizumab and two omalizumab trials were included, both of which were open-label. Odds ratios for fixed-effects and random-effects analyses were identical (0.71; 95% CI 0.26 to 1.89) and indicate no difference between reslizumab and omalizumab in the proportions of patients hospitalised due to exacerbations. Limitations are the open-label nature of the omalizumab studies, and relatively low rates of hospitalisation events. Also, the ITC Report presents the percentage of patients hospitalised due to exacerbations in each arm of the four trials and this shows that the BSC arms of the omalizumab trials had higher hospitalisation rates than the placebo arms of the reslizumab trials.

The ITC results for changes in lung function (FEV1) at 16±4 weeks are based on five reslizumab trials and three omalizumab trials. Two of the omalizumab trials were open-label and the company conducted a sensitivity analysis excluding these, i.e. leaving only one omalizumab trial in the analysis. The analysis of all trials gave a fixed-effects mean difference in the change from baseline of 0.00 L (95% CI –0.07 to 0.08) and the random-effects analysis gave a mean difference of 0.01 L (95% CI –0.13 to 0.01), whilst the analysis excluding open-label trials gave a fixed-effects mean difference of –0.13 L (95% CI –0.3 to 0.04). The results indicate a lack of clinically significant or statistically significant differences between reslizumab and omalizumab in the FEV1 change from baseline to 16±4 weeks.

ITC analysis of changes in lung function at 52 weeks was based on two reslizumab trials and only one omalizumab trial. The fixed-effects analysis mean difference in FEV1 change from baseline was –0.19 L (95% CI –0.25 to –0.13), indicating that, over 52 weeks, FEV1 was improved statistically significantly more by omalizumab than by reslizumab. However, the company's ITC Report comments that the difference (0.19 L) was less than that considered to be clinically important (0.2 L).

ITC analysis of discontinuations due to adverse events up to 16 weeks was based on three reslizumab and two omalizumab trials. The odds ratios for fixed-effects and random-effects analyses were identical (1.13; 95% CI 0.17 to 7.62) and indicate no significant difference between reslizumab and omalizumab in the odds of experiencing discontinuations due to adverse events up to 16 weeks.

ITC analysis of discontinuations due to adverse events up to 52±4 weeks was based on two reslizumab trials and one omalizumab trial. The fixed-effects estimate of the odds ratio (0.48; 95% CI 0.16 to 1.43) indicates no difference between reslizumab and omalizumab in the odds of experiencing discontinuation due to adverse events up to 52±4 weeks.

ITC analysis of serious adverse events up to 16 weeks was based on three reslizumab trials and four omalizumab trials. The fixed-effects and random-effects odds ratios were identical (1.04; 95% CI 0.4 to 2.68) and indicate no difference between reslizumab and omalizumab in the odds of experiencing serious adverse events up to 16 weeks.

ITC analysis of serious adverse events up to 52±4 weeks was based on two reslizumab trials and two omalizumab trials. The company conducted a sensitivity analysis excluding one open-label omalizumab trial, i.e. leaving only one omalizumab trial in the analysis. The fixed-effects and random-effects odds ratios for the full analysis on all trials were identical (0.71; 95% CI 0.4 to 1.24) and indicate no difference between reslizumab and omalizumab in the odds of experiencing serious adverse events up to 52±4 weeks. The fixed-effects odds ratio for the analysis excluding the open-label trial (0.80; 95% CI 0.43, 1.48) also indicates no difference.

ITC analysis of changes in HRQoL (AQLQ scores) at 16±4 weeks were based on four reslizumab trials and one omalizumab trial. The fixed-effects mean difference in the change from baseline (–0.56; 95% CI –0.92 to –0.20) statistically significantly favours omalizumab over reslizumab, although the ITC Report does not mention this.

ITC analysis of changes in AQLQ scores at 52±4 weeks were based on two reslizumab trials and one omalizumab trial. The fixed-effects mean difference in the change from baseline (0.10; 0=95% CI –0.11 to 0.31) indicates no significant difference in the change in AQLQ score between the reslizumab and omalizumab groups.

As noted below (Commentary on the robustness of the submitted evidence) the ERG has serious concerns about the methodological quality of the company's ITC and these should be borne in mind when interpreting the above results.

Results of the ITC do not directly inform the company's economic analysis. In the economic analysis section of the CS it is stated that rate ratios for exacerbations as employed in the company's economic analysis were derived from the ITC (which is referred to as an NMA – network meta-analysis). However, this information is not given in the company's ITC Report.

Summary of submitted cost effectiveness evidence

A systematic search was conducted by the company to identify economic evaluations of pharmacological interventions for adults with severe eosinophilic asthma. The review excluded RCTs and non-UK economic evaluations. The company identified five relevant studies, four comparing omalizumab to BSC and one comparing mepolizumab to BSC.

The company's de novo cost effectiveness analysis used a Markov model to estimate the cost effectiveness of reslizumab compared to BSC and omalizumab. The model adopted a time horizon of 60 years and a cycle length of four weeks. The model consisted of six mutually exclusive health states: controlled asthma, uncontrolled asthma, moderate exacerbation, severe exacerbation, asthma-related death, and all-cause mortality. Patients in the model receiving reslizumab and omalizumab were assessed at 16 weeks, and those classed as non-responders were assumed to discontinue treatment. Patients were also assessed at 52 weeks and each year thereafter, discontinuing treatment if they remained in either an exacerbation or uncontrolled state continuously for one year. As recommended by NICE, a discount of 3.5% was used for both costs and health outcomes. The analyses were conducted from the perspective of the NHS and PSS.

Patients transitioned between health states in the model according to transition probabilities. For the reslizumab and BSC treatment arms, the transition probabilities were computed using patient-level data from the pivotal reslizumab trials (3082 and 3083). The sample used to estimate the transition probabilities was the subgroup of adult patients (aged 18 years or older), at step 4 or 5 in the GINA pathway, who had experienced at least 2 exacerbations in the preceding year. The company adjusted the exacerbation probabilities estimated from the ≥2 exacerbation subgroup to reflect the rate of BSC exacerbations observed in the year before randomisation in the subgroup of interest (≥3 exacerbations in the base case analysis). For the omalizumab treatment arm, rates of exacerbation after 16 weeks were based on an analysis for responders in the INNOVATE trial. The source of the exacerbation rate for omalizumab prior to 16 weeks was unclear in the CS. Rates of asthma control and response to treatment for omalizumab were assumed equal to those for reslizumab.

The company conducted a systematic review for costs and HRQoL. The company used HRQoL data from studies by Willson and colleagues and Lloyd and colleagues. These studies were for patients with asthma at GINA steps 4 and 5 and reported EQ-5D data using the UK tariff.

Reslizumab is administered via intravenous administration and the recommended dose of reslizumab, based on patient weight, is 3.0 mg/kg given once every 4 weeks. Resilizumab is anticipated to have a confidential patient access scheme. Omalizumab is currently provided on the NHS with a confidential patient access scheme.

Results of the economic model are presented as the incremental cost per quality adjusted life year (QALY). The patient population eligible for treatment differs between omalizumab and reslizumab and so the company presents two analyses for reslizumab versus BSC and for reslizumab versus omalizumab. The results of the cost effectiveness analyses at the list price for omalizumab and the PAS price for resilizumab showed an incremental cost effectiveness ratio (ICER) of £24,907 per QALY for reslizumab compared to BSC and omalizumab is extendedly dominated by BSC.

The company performed a range of deterministic and probabilistic sensitivity analyses to assess model uncertainty. The ICER remained below £30,000 per QALY in all deterministic sensitivity analyses, with the exception of reducing the time horizon to five years. The analyses are most sensitive to the rate of exacerbations for the BSC arm. The company provided analyses for subgroups according to the number of exacerbations experienced in the previous year, by calibrating the transition probabilities to the exacerbation health states using an 'exacerbation multiplier'. The ICER varied between £33,774 per QALY for patients who had experienced ≥2 exacerbations in the preceding year and £20,006 per QALY for patients who had experienced ≥4 exacerbations.

The probabilistic sensitivity analysis (PSA) estimated a [redacted] and [redacted] probability that reslizumab is cost effective at a willingness to pay threshold of £20,000 and £30,000 per QALY gained, respectively.

Commentary on the robustness of submitted evidence

Strengths

Clinical effectiveness

The company conducted a systematic review for relevant trials and appears to have identified all relevant evidence for reslizumab and the majority of evidence for omalizumab. The included trials of reslizumab are of generally good quality and the company provided a quality assessment for four out of the five trials. We largely agree with the company's assessments of trial quality (apart from some issues around missing data, particularly in the trials 3081 and

3084). The company provided clinical study reports and publications in support of the CS. The CS and the company's ITC report are generally well structured with clear tabulation of trial characteristics and results.

Economic analysis

A systematic review was conducted to identify cost-effectiveness, HRQoL and cost studies and values from this review were utilised in the model. The model structure is based on a published model in severe asthma and is representative of the clinical pathway for patients with severe asthma. The trials used for the effectiveness evidence are of generally good quality.

Weaknesses and areas of uncertainty

Clinical effectiveness

The main limitation of the clinical trials is that their duration (15 to 52 weeks) is relatively short given that asthma is a chronic condition. In one of the trials (3084), 80% of the population had blood eosinophils <400 per μL which differs from the inclusion criterion for the other trials (blood eosinophils ≥400 per μL).

The company (despite a request for clarification from the ERG via NICE) is unclear about the relevance of the trial Res-5-0010: this trial was identified in the systematic review, then excluded by the company, then subsequently included in some outcome analyses. For the AQLQ outcome assessed at 16 weeks this trial was excluded from the direct comparison but included in the ITC.

Although the trials involved approaches to account for missing data, such as sensitivity analyses, the reported sample sizes for the analysed outcomes do not concur with the number randomised and reasons for missing data are not explained. There are also inconsistencies in the sample sizes reported in the CS for the individual clinical trials and the direct comparison meta-analysis.

The ERG has a number of concerns about the company's ITC:

- The 'feasibility' process for selecting trials for inclusion is poorly described in the ITC report. ~~*For the AQLQ outcome assessed at 16±4 weeks the trial Res-5-0010 is included in the ITC of reslizumab versus omalizumab but excluded from the direct comparison of reslizumab versus placebo, without any explanation.*~~
- The company's process for selecting trials based on their definitions of clinically significant exacerbations appears inconsistent, meaning that several omalizumab trials may have been unnecessarily excluded from analysis.
- The company has not considered any possible differences between placebo, BSC, optimised asthma therapy and control groups in the omalizumab trials and it is therefore unclear whether these different arms are adequately homogeneous to serve as a common comparator in the ITC.
- The company's trials provide evidence for placebo effects but the CS does not consider whether this has any implications for the assumption that placebo is equivalent to BSC.
- ~~*The CS selectively presents only fixed-effects model results for the analysis of clinically significant exacerbation rates when a random-effects analysis should at least have been presented for comparison.*~~
- The reported sample sizes for the reslizumab trials analysed in the ITC are different to those for the same trials when analysed for the same outcomes in the direct comparison; furthermore, for some outcomes sample sizes are markedly smaller than the number randomised and (where defined) smaller than the 'full analysis set'.
- *[Note added after final submission of this ERG report to NICE: The company clarified during the factual inaccuracy check process that sample sizes for the ITC analyses were the same as those for their direct comparison meta-analysis but were reported incorrectly in the ITC Report (the ERG cannot corroborate this). The company also clarified that trial Res-5-0010 was not included in the AQLQ ITC analysis, although the ITC Report states that it was. These discrepancies do not materially affect the conclusions of this report, since other uncertainties in the results of the ITC analysis remain].*

Overall, based on these limitations we advise that the ITC results should be viewed with caution since they could be at high risk of bias.

Economic analysis

The systematic review of economic studies, HRQoL and resources has limiting exclusion criteria: all RCTs were ineligible for inclusion; HRQoL and costs may only come from observational studies; economic evaluations may only be UK models; and if a study reported on mixed adult and juvenile populations or mixed severity populations they were excluded.

The model structure is not directly comparable to other technology appraisals (omalizumab and mepolizumab)

The model applies an exacerbation multiplier to increase the rate of exacerbations, to a similar level as seen in the year preceding the trial. It is not clear if applying this multiplier is appropriate.

The definitions of exacerbations were not consistent between the HRQoL studies and the definition used in the model, which is likely to lead to an overestimate in the severity of the exacerbation utility values.

Summary of additional work undertaken by the ERG

The ERG conducted the following additional analyses to investigate changes to the model results:

- Changes to the exacerbation rate for BSC to reflect the observed exacerbation rate in the reslizumab clinical trials;
- Alternative utility values for the exacerbation health states;
- Alternative health state costs ;
- shorter monitoring duration for omalizumab.
- An alternative base case analysis for reslizumab compared to BSC and omalizumab, consisting of a combination of the analyses above.

Changing the exacerbation rate for BSC to reflect the actual exacerbation rate in the clinical trials has a significant impact on the model results and increases the ICER for reslizumab vs BSC to £50,878 per QALY. The other analyses have a smaller impact on the model results. The ERG's alternative base case comparison for reslizumab compared to BSC produces an ICER of £57,356 per QALY. In comparison to reslizumab, omalizumab remains extendedly dominated.

1 Introduction to the ERG Report

This report is a critique of the company's submission (CS) to NICE from Teva UK Limited on the clinical effectiveness and cost effectiveness of reslizumab (brand name CINQAERO) for the treatment of adults with asthma who have elevated blood eosinophils and whose asthma is inadequately controlled by inhaled corticosteroids (ICS). Reslizumab plus best standard of care (BSC) is compared against BSC alone and also against omalizumab plus BSC. In this report the Evidence Review Group (ERG) identifies the strengths and weakness of the CS. Clinical experts were consulted to advise the ERG and to help inform this review.

Clarification on some aspects of the CS was requested from the manufacturer by the ERG via NICE on 10/08/2016. A response from the company via NICE was received by the ERG on 30/08/2016 and this can be seen in the NICE committee papers for this appraisal.

2 BACKGROUND

The CS provides an appropriate description of severe asthma, highlighting the heterogeneity of the disease.

2.1 Summary & critique of the company's description of the underlying health problem

Asthma is a chronic inflammatory disease associated with airway inflammation, variable airflow obstruction and airway hyper-responsiveness and affects around 5.4 million people in the UK (1 in 11 children and 1 in 12 adults). The UK has some of the highest asthma rates in Europe. The disease accounts for high numbers of consultations in primary care, out-of-hours services and hospital emergency departments. The CS cites figures from 2011-2012 for hospital admissions and 2000-2005 for asthma mortality rates in the UK. More up-to-date figures report that there were 60,636 hospital admissions for asthma in England in 2013-2014, and 138,140 bed days and 80,990 finished consultant episodes in 2015.[1] Asthma was responsible for 1216 deaths in 2014, with a mean number of three deaths per day from the disease.[2] Asthma costs the NHS an estimated £1 billion a year, with the burden being driven by severe cases.[3]

Asthma is characterised by variable and recurring symptoms. An asthma 'exacerbation' or 'attack' refers to people with asthma experiencing a worsening of their symptoms and airway function, with an increase in breathlessness, wheezing, chest tightness, sputum production and/or cough. Asthma exacerbations can have a considerable negative impact on patients' health-related quality of life (HRQoL), affecting activities such as work, exercise and travel, as well as reducing their sense of wellbeing due to fear of having further symptoms or exacerbations.[4]

Most patients manage their asthma by following guidance from physicians based on a stepwise approach to treatment as recommended by the British Thoracic Society (BTS) and the Scottish Intercollegiate Guideline Network (SIGN).[5] The BTS/SIGN treatment approach is very similar to the stepwise approach recommended by the Global Initiative for Asthma (GINA)[6] (Table 1). As explained further below (section 2.2), patients should start treatment at the step most appropriate to the initial severity of their disease and maintain asthma control by stepping up treatment when control is poor and stepping down when control is good.

Eosinophilic asthma is a phenotype of severe asthma that is associated with elevated levels of eosinophils (a type of white blood cell) in tissues and sputum, and may be accompanied by eosinophilic nasal polyps. Eosinophils play a role in airway inflammation, and increased concentrations of eosinophils (referred to as eosinophilia) are associated with increased frequency of exacerbations and poor disease control.[7] The population of patients who have asthma with elevated blood eosinophils is equivalent to patients who are at Step 4 and or Step 5 of the BTS/SIGN and GINA treatment pathways (Table 1), and these patients meet GINA classification criteria for having severe asthma (Table 2).

Despite best therapeutic attempts, for a small subgroup of around 5-10% of patients with severe eosinophilic asthma, the disease remains inadequately controlled at Steps 4 and 5. A small proportion of these patients on best standard of care (BSC) who have severe persistent IgE-mediated asthma may be eligible for treatment with omalizumab; however, for the majority of patients whose asthma is not controlled at Steps 4 and 5 treatment options are limited, and consist currently of further increasing the dose of inhaled corticosteroids (ICS) or adding oral corticosteroids (OCS). Long-term use of ICS is associated with well-known adverse effects, including, among others, reduced bone mineral density[5] and diminished corticosteroid sensitivity.[8]

Reslizumab, used in addition to BSC, is a potential new treatment option for patients whose severe eosinophilic asthma is not controlled at Steps 4 and 5, particularly those who are not eligible to receive omalizumab.

2.2 Summary & critique of the company's overview of current service provision

The CS provides an overview of the clinical pathway of care, which is primarily based on the BTS/SIGN guidelines.[5] The care pathway described in the CS is relevant and appropriate to the decision problem in the NICE scope. The stepwise approach recommends that when control of the condition is poor, treatment doses should be increased and/or other controller medications should be added, and that treatment should be stepped down when control is good or improved (see Table 1). As pointed out in the CS, there are no specific guidelines available for the management of people with severe eosinophilic asthma inadequately controlled by ICS. The CS points out, though, that this population falls within the European Respiratory Society/American Thoracic Society (ERS/ATS) Task Force and GINA guidelines' definitions of severe asthma.[9] The ERG agrees with this. The GINA definition of asthma severity is shown in Table 2. The GINA guidelines (Table 1) offer a similar stepwise treatment approach to that specified in the BTS/SIGN guidelines. The CS states that the population of interest in this appraisal would receive the same management approaches as set out in the last two steps of the GINA and BTS/SIGN guidelines (i.e. steps 4 and/or 5), which are used to treat severe asthma (as defined in Table 2).

Table 1 Asthma treatment stepwise approach

Step	BTS/SIGN recommended stepwise approach to treatment in adults (CS Table 8)	GINA recommended stepwise approach to treatment (CS Table 9)
1	*Mild intermittent asthma* Inhaled SABA as required	• Other controller options: Consider low dose ICS • Reliever: SABA as needed
2	*Regular preventer therapy* • Add ICS (200–800 µg/day[a]) Starting dose should be appropriate to severity of disease (400 µg is appropriate for many patients)	• Preferred controller: Low dose ICS • Other treatment options: o Leukotriene receptor agonist o Low dose theophylline[b] • Reliever: SABA as needed

Step	BTS/SIGN recommended stepwise approach to treatment in adults (CS Table 8)	GINA recommended stepwise approach to treatment (CS Table 9)
3	*Initial add-on therapy* Add inhaled LABA. Assess asthma control and adjust treatment according to the following: • If control remains inadequate, continue LABA and increase the dose of ICS to 800 µg/day if not already on this dose • If there is no response to LABA, stop this drug and increase the dose of ICS to 800 µg/day • If control still remains inadequate, try leukotriene receptor antagonist or slow-release theophylline	• Preferred controller: Low dose ICS/LABA[c] • Other controller options : o Medium/high dose ICS o Low dose ICS + leukotriene receptor agonist (or + theophylline[b]) • Reliever: SABA as needed or low dose ICS/formoterol[d]
4	*Persistent poor control* • Consider increasing the dose of ICS up to 2000 µg/day • Consider adding a fourth drug (e.g. leukotriene receptor agonist, slow-release theophylline or beta2-agonist tablet)	• Preferred controller: Medium/high dose ICS/LABA • Other controller options : o Add tiotropium[b, e] o High dose ICS + leukotriene receptor agonist (or + theophylline[b]) • Reliever: SABA as needed or low dose ICS/formoterol[d]
5	*Continuous or frequent use of oral steroids* • Use daily steroid tablet at the lowest dose that provides adequate control • Maintain high-dose ICS at 2000 µg/day • Consider other treatments to minimise the use of steroid tablets • Refer patient for specialist care	• Preferred controller: Refer for add-on treatment (e.g. tiotropium, omalizumab, mepolizumab) • Other controller options : o Add low dose OCS • Reliever: SABA as needed or low dose ICS/formoterol[d]

ICS, inhaled corticosteroid; LABA, long-acting beta2-agonist; OCS, oral corticosteroid; SABA, short-acting beta-agonist.
[a] Beclometasone dipropionate (BDP) or equivalent
[b] Not for children aged <12 years.
[c] For children aged 6–11 years, the preferred Step 3 treatment is medium dose ICS
[d] Low dose ICS/formoterol is the reliever medication for patients prescribed low dose budesonide/formoterol or low dose beclometasone/formoterol maintenance and reliever therapy.
[e] Tiotropium by mist inhaler is an add-on treatment for patients with a history of exacerbations; it is not indicated in children aged <12 years

Table 2 GINA definition of asthma severity

Severity	Description (from CS Table 7)
Mild	Asthma that is well controlled with Step 1 or 2 treatment, i.e. with as-needed reliever medication alone, or with low-intensity controller treatment such as low dose ICS, leukotriene receptor antagonists or chromones.
Moderate	Asthma that is well controlled with Step 3 treatment, e.g. low dose ICS/LABA.
Severe	Asthma that requires Step 4 or 5 treatment, e.g. high-dose ICS/LABA, to prevent it from becoming uncontrolled, or that remains uncontrolled despite this treatment.

GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; LABA, long-acting beta-agonist.

A NICE clinical guideline 'Asthma Management' is currently under development and due to be published in 2017. However, this will not include 'biologics' (for example omalizumab) and therefore, as pointed out in the CS, it is also not expected to cover the anti-IL-5 antibodies (i.e. reslizumab and mepolizumab). The only NICE guidance available that includes the management of the severe asthma population relevant to the current technology appraisal is TA 278 (omalizumab for treating severe persistent allergic asthma).

As mentioned in the CS (section 3.5), a NICE quality standard on clinical best practice for diagnosis and treatment of asthma in people aged 12 years and older (QS25) was published in 2013,[10] and was updated in February 2016 to include a 2014 revision of the BTS/SIGN guideline on the management of asthma. The updated NICE QS25 defines asthma in adults as 'difficult asthma' if symptoms persist despite treatment at Steps 4 or 5 of the BTS/SIGN guideline, plus one of the following:

- an event of acute severe asthma which is life threatening, requiring invasive ventilation within the last 10 years
- requirement for maintenance oral steroids for at least six months at a dose ≥7.5 mg prednisolone per day or a daily dose equivalent of this calculated over 12 months
- two hospitalisations within the last 12 months in patients taking and adherent to high dose inhaled steroids (≥1000 µg of beclomethasone or equivalent)
- fixed airflow obstruction with a post bronchodilator FEV1 <70% of predicted normal.

The ERG notes that the NHS England A14 Service Specification for Severe Asthma,[11] which is not mentioned in the CS, states that there is currently no clear definition of severe asthma and no gold standard diagnostic test. It suggests that the BTS/SIGN guidelines definition above is

too general, and mentions an up-to-date definition proposed by the European Respiratory and American Thoracic Societies. Clinical expert advice received by the ERG suggests that the indications for severe asthma management are still in development.

According to the NHS England A14 Service Specification for Severe Asthma,[11] patients suspected of having severe asthma would be referred to receive a multidisciplinary assessment at a specialist severe asthma centre. Such a centre should be run by at least two consultant respiratory physicians with an interest in severe asthma. Multi-disciplinary assessment of the patient involves review by a physiotherapist, asthma nurse specialist, health psychologist, dietician, and allergist, and is conducted over two day-case visits. Pre-planned investigations include measures of airway inflammation and airways hyper-reactivity, which are only available at specialist centres. Once patients have received a diagnosis, the treatment decision and initial assessment of efficacy are carried out at the specialist centre. Treatment decisions include the patient's suitability for bronchial thermoplasty, omalizumab, or novel biological therapies as they become available. If trials of these drugs are successful at the specialist centre, then the drugs may be used outside of the specialist centre in the longer-term. The majority (approximately 70%) of patients with severe, difficult to control asthma will receive long-term follow up at a specialist centre, with an initial 3-month follow-up consultation and then reviews every six months if clinically stable. Referrals to specialist centres originate primarily from respiratory physicians in secondary care (but may also arise from primary care or after an episode in an intensive care unit).

The CS acknowledges (CS Table 6 and CS section 2.4.2) that patients will initially receive reslizumab and ongoing monitoring in specialist centres. The CS, however, does not clearly draw out the implications of this for patients and the NHS. Clinical expert advice to the ERG suggests that treatment in a specialist centre would incur extra costs for the NHS and patients. There are currently five such centres, with more specialist centres due to be rolled out in the future. However, according to clinical expert advice received by the ERG, the national commissioning structure is still in development.

Treatment options

As stated in the CS, there are limited treatment options for patients with severe asthma which remains inadequately controlled with medium to high dose ICS in combination with other controller medications. Continuing to increase ICS dose or adding OCS are options, but as high-

dose and long-term use of corticosteroids are associated with a range of adverse effects, the BTS/SIGN guidelines state that ICS and OCS should be used at the lowest doses at which asthma control is maintained and other treatments should be considered to minimise the use of steroid tablets.

For patients with severe persistent allergic (IgE-mediated) asthma (≥6 years) who need continuous or frequent treatment with oral corticosteroid (OCS) (defined as ≥4 in the previous year), NICE recommends the anti-IgE monoclonal antibody omalizumab as an add-on treatment option to optimised standard therapy (MTA, TA278).[12] The treatment recommendation is dependent on the manufacturer making omalizumab available with the discount agreed in the patient access scheme (PAS).[12] As explained in the CS, omalizumab does not target the eosinophilic (IL-5-mediated) phenotype and so is unsuitable for patients with severe eosinophilic asthma, unless these patients also have IgE-mediated asthma. According to the final NICE scope, omalizumab is suitable for people with severe persistent allergic IgE-mediated asthma with elevated blood eosinophils.[12]

The anti-IL-5 monoclonal antibody mepolizumab is licensed as an add-on treatment for severe refractory eosinophilic asthma in adults and is currently being apprised by NICE.

2.3 Summary & critique of the company's definition of the decision problem

Population

The patient population in the CS decision problem appears consistent with the NICE scope, which refers to 'adults with asthma with elevated blood eosinophils inadequately controlled by inhaled corticosteroids'. This is an appropriate population for the NHS, as these patients currently have limited treatment options. The NICE scope does not define 'elevated blood eosinophils', but according to clinical expert advice to the ERG, although there are difficulties in specifying the degree of severity of eosinophilia, the threshold for elevated blood eosinophils of ≥400 cells/μL employed by the company (consistent with the pivotal clinical trials of reslizumab) is reasonable.

The CS states that the population is those aged 18 years or older. We note that the clinical trials included in the company's review of clinical effectiveness included patients who were aged 12 years and older. However, the mean age of patients in all the included trials was above 40 years.

Intervention

Reslizumab is intended to be used in addition to best standard of care (BSC). The indication, restrictions and marketing status of reslizumab are summarised by the company (CS Table 2) and are reproduced here in Table 3.

Reslizumab is a humanised monoclonal anti-IL-5 antibody (IgG4/κ) 'indicated as add-on therapy in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose ICS plus another medicinal product for maintenance treatment'.[13] IL-5 is a pro-inflammatory cytokine which plays a key role in the differentiation, maturation, recruitment and activation of eosinophils. Reslizumab binds to human IL-5, blocking its biological function; consequently, survival and activity of eosinophils are reduced (Summary of Product Characteristics [SmPC]).[13] Given that high levels of eosinophils in sputum and bronchial biopsies are associated with poor asthma control,[14] blocking IL-5 function can reduce the frequency and severity of asthma exacerbations.

The CS states that it is anticipated that reslizumab will be initiated and monitored in specialist centres; reslizumab should be prescribed by physicians experienced in the diagnosis and treatment of the licensed indication and administered intravenously by a healthcare professional; and patients should be observed over the duration of the infusion and for an appropriate period of time afterwards.

According to the SmPC, reslizumab is only indicated for intravenous infusion and should be administered in a healthcare setting by a healthcare professional prepared to manage anaphylaxis. The recommended dosage regimen is 3 mg/kg once every 4 weeks by intravenous infusion over 20-50 minutes, with the solution being available in 100 mg/10 mL (10 mg/mL) single-use vials. If a planned reslizumab infusion is missed, dosing should resume as soon as possible on the indicated dose and regimen. A double dose must not be administered to make up for a missed dose. The ERG agrees that the description of reslizumab in the company's

decision problem, including the dosing regimen, is consistent with the proposed licensed indication as stated in the SmPC.

At the time of the company's submission, the European marketing authorisation for reslizumab was awaited. Market authorisation was granted in August 2016 (Table 3). Approval by the US Food and Drug Administration (FDA) was granted in March 2016 and reslizumab was launched in the US in April 2016. However, licensed indications in the USA stipulate that reslizumab is not indicated for treatment of other eosinophilic conditions, relief of acute bronchospasm or status asthmaticus (Section 5.2).[15]

The CS states that the planned launch for reslizumab in the UK is [redacted].

Table 3 Technology being appraised (CS Table 2)

UK approved name and brand name	UK approved name: Reslizumab Brand name: CINQAERO
Marketing authorisation/ CE mark status	• Regulatory submission to EMA: The application was submitted on 30 June 2015 and the procedure started on 23 July 2015. • CHMP positive opinion was received on 23 June 2016. • European marketing authorisation was granted in August 2016.
Indications and any restriction(s) as described in the summary of product characteristics	Reslizumab is indicated as add-on therapy in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose ICS plus another medicinal product for maintenance treatment (Section 5.1 of the SmPC). The contraindications listed in the SmPC are: • Hypersensitivity to the active substance • Hypersensitivity to any of the following excipients: sodium acetate trihydrate; acetic acid glacial; sucrose; water for injections
Method of administration and dosage	Intravenous infusion only. Reslizumab must not be administered by the subcutaneous, oral or intramuscular route. Reslizumab is available as a 10 mg/mL concentrate for solution for infusion. Each vial contains 100 mg of reslizumab in 10 mL (10 mg/mL). The recommended dose of reslizumab, based on body weight, is 3.0 mg/kg, given once every four weeks.

CHMP: Committee for Medicinal Products for Human Use; EMA: European Medicines Agency; ICS: inhaled corticosteroid; SmPC: Summary of Product Characteristics

Comparators

The comparators for reslizumab as add-on to BSC that are considered in the current submission are:

- BSC alone (for patients with an eosinophilic phenotype of asthma who are not eligible for omalizumab)
- Omalizumab + BSC (for patients in the 'overlap' population – i.e. those with IgE-mediated asthma who also have elevated blood eosinophils)

BSC (placebo arm) in the CS is referred to as high dose ICS in combination with other controller medications, with or without OCS. In addition, the BTS/SIGN guidelines are cited stating that BSC relies on the use of a Personal Asthma Action Plan, the avoidance of environmental/dietary triggers and the use of recommended medications. To clarify medication use in the placebo arm of the pivotal trials RCT 3082 and 3083, the company provided tables of medication use for patients in the placebo arm (clarification request A4, Tables 1 to 3).

Outcomes

The outcomes reported in the CS are clinically meaningful and are consistent with the NICE scope, although four outcomes specified in the scope are not reported in the CS as they were either not reported in the reslizumab trials (use of OCS, patient and clinician evaluation of response, time to discontinuation) or were very rare events (mortality – only one death occurred across the five included trials). Two additional outcomes not specified in the NICE scope are presented in the CS: changes in use of short-acting beta agonists (SABA) and changes in blood concentrations of eosinophils.

The CS states that the reason data on OCS use were not available is that the dose of OCS in two of the pivotal studies (3082 and 3083) had to remain stable throughout the trial and therefore this was not reported as an outcome; whilst in the remaining three trials OCS use was not allowed. However, clinical experts advising the ERG mentioned that OCS use is potentially an important factor, as, in addition to their impact on adverse events, oral steroids are a significant cost driver in this population.

The NICE scope mentions "incidence of clinically significant exacerbations, including those which require unscheduled contact with healthcare professionals or hospitalisation," but does

not define clinically significant exacerbations. The CS decision problem refers to “clinical asthma exacerbations” which were reported in the reslizumab trials and implies that the definition of these is consistent with the NICE scope. We agree that the company’s definition of exacerbations in reslizumab trials is consistent with the scope.

Economic analysis

The cost effectiveness of treatments is expressed in the CS in terms of the incremental cost per quality adjusted life year (QALY) gained (as specified in the final NICE scope). Base case analyses used a 60-year (lifetime) time horizon and 3.5% annual discounting of costs and outcomes. The economic analysis was consistent with the NICE reference case and costs were considered from an NHS and Personal and Social Services (PSS) perspective.

Other relevant factors

In the company’s economic analysis, the CS states that, based on the advice of (an unspecified number of) clinical experts, adult patients at GINA Steps 4 or 5 (Table 1) who had experienced ≥3 asthma exacerbations in the preceding year were considered to be the most appropriate subgroup for the base case analysis. This is because these patients would benefit the most from treatment with reslizumab. That is, they were patients with severe eosinophilic asthma and a history of exacerbations. The ERG notes that the majority of the patients in the pivotal clinical trials did not experience ≥3 asthma exacerbations in the preceding year, and so the economic model includes only a subgroup of patients in these trials.

Two further subgroups with lower and higher exacerbation rates were included in scenario analyses:

- Adult patients at GINA Steps 4 or 5 who had experienced ≥2 exacerbations
- Adult patients at GINA Steps 4 or 5 who had experienced ≥4 exacerbations

These subgroups were not specified in the NICE scope. However, the scenarios offer insight into the cost-effectiveness of reslizumab when the exacerbation threshold for including patients in the analysis is lowered.

Equality issues

The CS states that 'no issues related to equality were identified in the NICE scope' (CS section 3.8). However, the ERG notes that it might be difficult for patients to attend a specialist severe asthma centre on a four-weekly basis, as there are currently only five centres in England and, according to a clinical expert consulted by the ERG, these have waiting lists of up to 12 months.

Patient access scheme

The CS states that a 'simple' PAS has been submitted to PASLU and the Department of Health and is currently under review' (CS section 2.3.1). The suggested anticipated reslizumab list price is £499.99 (100 mg vial) or £124.99 (25 mg vial), while the anticipated PAS price will be £[redacted] (100 mg vial) or £[redacted] (25 mg vial) (CS Table 6).

3 CLINICAL EFFECTIVENESS

3.1 Summary & critique of the company's approach to systematic review

The company conducted two systematic reviews, one for evidence on the clinical effectiveness of reslizumab and omalizumab, and the other for HRQoL, resource use, and economic evidence. A full description and critique of the company's systematic review of HRQoL, resource use and economic evidence is provided within the Cost Effectiveness section of this report, in section 4.2.

The systematic review of clinical effectiveness evidence is described in section 4.1 of the CS and the search strategy is provided in CS Appendix 2. The systematic review was used to identify evidence both for the intervention (reslizumab) and for the comparator (omalizumab) and therefore it informed the company's direct comparison meta-analysis of reslizumab trials as well as their indirect treatment comparison (ITC) of reslizumab against omalizumab. The ITC analysis was provided by the company in a separate report prepared by an external agency (Amaris)[16] (hereafter referred to as the ITC Report) and this includes duplicate descriptions of the systematic review methods (ITC Report section 2.1) and the search strategy (ITC Report Appendix 2).

3.1.1 Description of the company's search strategy

The company has clearly specified the bibliographic sources searched and the dates of the searches, providing sufficient details to enable reproduction of the searches. We consider that the searches were comprehensive and well-designed. They included a combination of MeSH or EMTREE and free text terms, which is appropriate, and used a range of terms that cover the disease area, interventions, and study types of interest. An exception to this is that the EU trade name of reslizumab (Cinqaero) was not used among the intervention search terms, while the US trade name (Cinquil) was. We do not believe that this is likely to have impacted on whether the searches found all relevant evidence. The searches were restricted to the English language, which is reasonable. No date restrictions were placed on the searches.

The company searched an appropriate range of databases: MEDLINE, Embase and the Cochrane Library. Hand searches for conference abstracts in databases not indexed by Embase were also carried out, covering the European Respiratory Society (ERS), American Thoracic Society (ATS), British Thoracic Society (BTS), American College of Chest Physicians (CHEST) and the American Academy of Allergy, Asthma and Immunology (AAAI). Clinicaltrials.gov and HTA submissions were also searched. Additionally, a range of relevant websites were searched, including those of organisations that hold relevant conferences. We consider that the company has searched a wide range of and sufficient number of relevant sources for evidence.

A minor criticism of the clinical effectiveness searches is that they were five months out-of-date when received by the ERG, having been conducted in February 2016. We did not re-run the searches using the company's search strategy, but carried out simple searches on MEDLINE and Embase to identify if any further reslizumab and omalizumab studies had been published since February 2016. We used the following search terms:

- Reslizumab or Cinquil or Cinqaero
- (Omalizumab or Xolair or rhuMAb-E25) and asthma

We limited the searches to the English language and references published in 2016. For the omalizumab searches we additionally limited them to randomised controlled trials, phase 2 clinical trials and phase 3 clinical trials, to reduce the number of results.

Our searches did not find any additional studies of reslizumab, so it is likely that the CS includes all relevant reslizumab studies. Our searches for recently published omalizumab studies identified one potentially relevant RCT,[17] published online on 18th February 2016 (this was

published after the company's database searches for clinical effectiveness evidence, which were conducted on 2nd February 2016). This was an RCT of omalizumab versus placebo in Chinese patients with moderate to severe allergic asthma and a serum total IgE level of 30-700 IU/mL but it did not report whether any patients had elevated blood eosinophils. The % predicted FEV1, ACQ and AQLQ were among the outcomes measured. We also identified a conference abstract, published in April 2016, that appears to report findings from this trial.[18] No other potentially relevant omalizumab studies were identified. It therefore appears that although the searches used to inform the systematic review in the CS were moderately out-of-date, they are likely to have captured all relevant reslizumab and almost all relevant omalizumab trials.

The company did not explicitly mention in the CS whether or not they had searched for ongoing studies of reslizumab and did not specify any specific trials databases searched other than Clinicaltrials.gov. The CS states (section 4.14) that there are "no completed or ongoing company-sponsored studies from which new evidence for reslizumab in patients with asthma and elevated blood eosinophils will become available in the next 12 months" (CS p. 176). It is unclear therefore if there are any trials not sponsored by the company that may complete within the next 12 months. The ERG searched clinicaltrials.gov for ongoing studies of reslizumab. The ongoing studies were checked by one reviewer. No relevant ongoing studies were identified.

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection

The CS provides a clear overview of the inclusion and exclusion criteria for the systematic review of clinical effectiveness evidence (CS Table 11). The criteria appear to be in line with the marketing authorisation, the final NICE scope and the company's decision problem. While only RCTs were identified in searches, a company-sponsored single-cohort study amalgamating patients from three of the RCTs was included in the CS to provide evidence on reslizumab safety.

The setting (involving specialist severe asthma centres in England) was not specified as an inclusion criterion; this is reasonable given that the setting is implicit from the population eligibility criterion (severe asthma). The company excluded publications in non-English languages. The rationale for this is not explained in the CS and the potential for language bias is not discussed.

The CS provides a PRISMA diagram indicating the numbers of references included and excluded at each stage of the systematic review (CS Figure 1). This is reproduced in Figure 1. The total number of publications included in the systematic review was 21. This refers to trials of reslizumab and also trials of omalizumab, but only publications reporting the RCTs of reslizumab are mentioned in the list of relevant trials (CS Table 12). Information about the omalizumab trials is given in the separate ITC Report,[16] although there is no indication of this in the CS.

The CS (section 2.3, and Table 5 within CS Appendix 2) lists the authors and titles of 191 references which were excluded at the full-text screening step, but does not provide publication sources. The company provided this information in an Excel spreadsheet in response to a request from the ERG via NICE (clarification A8). Fifteen of these 191 references were excluded as the company was unable to retrieve them for full-text review of the inclusion criteria.

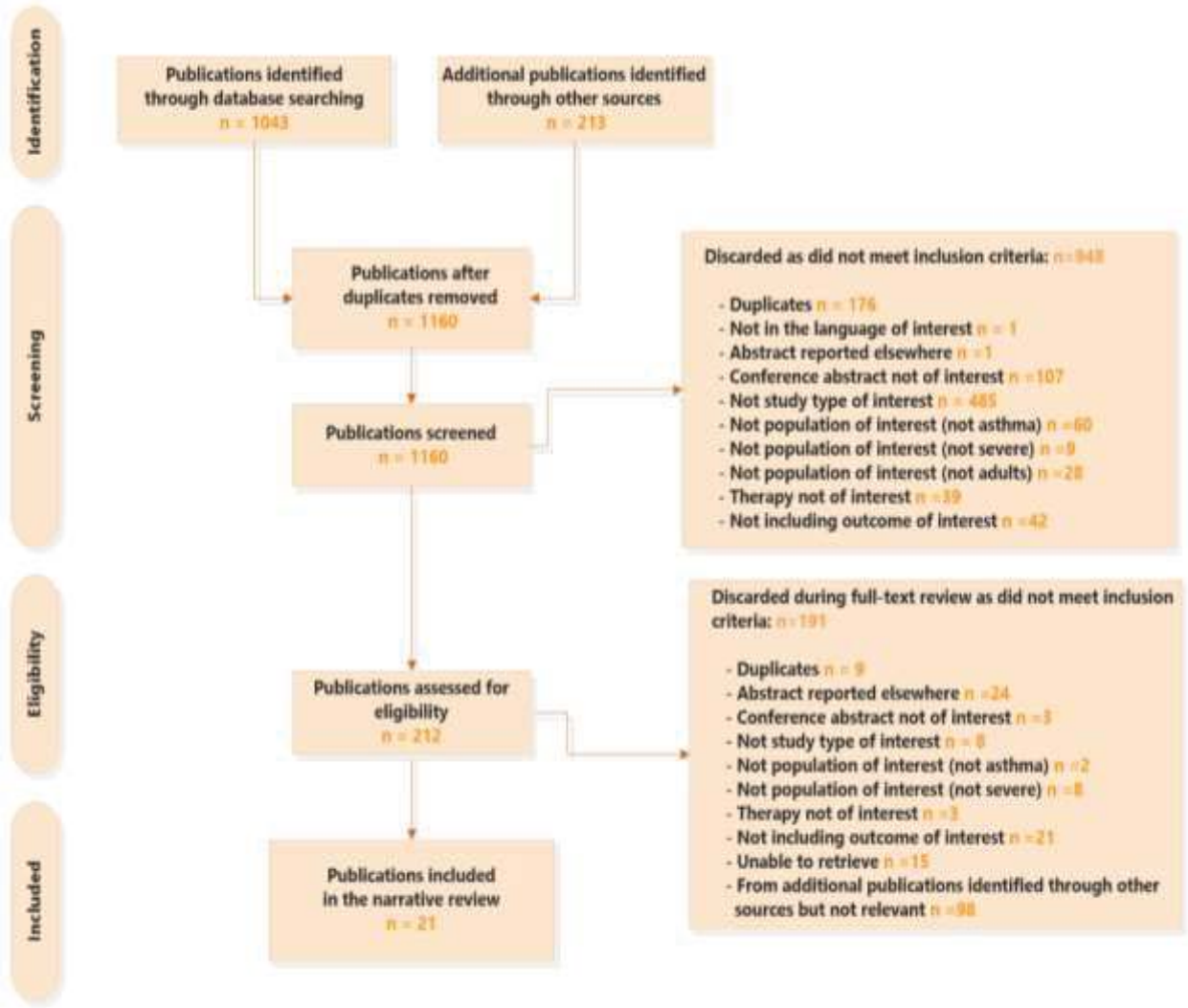


Figure 1 PRISMA diagram for the systematic review of clinical evidence

The CS does not mention any potential bias that may have arisen in relation to the searches or inclusion/exclusion criteria. However, the systematic review processes appear to have been robust, with eligibility screening having been conducted by two reviewers (CS section 4.1.2), which would reduce the risks of errors and bias.

3.1.3 Identified studies

Of the 21 RCTs identified by the company in their systematic review of clinical effectiveness, five were trials of reslizumab versus placebo (both in addition to BSC), and 16 were trials of omalizumab versus BSC (reported separately in the ITC Report[16]).

Four of the five reslizumab RCTs were phase III trials and one (Res-5-0010) was a phase II trial:

- trials 3082 and 3083, both reported by Castro et al.[19]
- trial 3081 reported by Bjermer et al.[20]
- trial 3084 reported by Corren et al.[21]
- Res-5-0010 reported by Castro et al.[22]

Trials 3082 and 3083 were identical 12-month, randomised, double-blind, placebo-controlled trials evaluating the efficacy and safety of reslizumab (3.0 mg/kg) in the reduction of clinical asthma exacerbations in patients aged 12-75 years with eosinophilic asthma.[19] These trials are presented first in the CS and are referred to in this report as the company's pivotal trials. The two pivotal trials had longer duration than the three other three trials and they also used a different definition of asthma exacerbations compared to the three other trials.

Trial 3081 was a 16-week randomised, double-blind, placebo-controlled, three-arm trial (0.3 mg/kg, 3.0 mg/kg and placebo), evaluating the efficacy and safety of reslizumab as treatment for patients aged 12-75 years with eosinophilic asthma.[20] The trial arm with less than the dose applied for in the licence (i.e. 0.3 mg/kg) is not relevant to this submission and is not discussed further in this report.

Trial 3084 was a 16-week, randomised, double-blind, placebo-controlled trial evaluating the effect of reslizumab (3.0 mg/kg) in patients aged 18-75 years with moderate to severe eosinophilic asthma that was poorly controlled with inhaled corticosteroids.[21] This RCT is presented separately to the other three company-sponsored RCTs in the CS 'due to different eligibility criteria'. Mean blood eosinophils at baseline ranged between 277–281 cells/μL for the treatment groups, with an overall range of 0–1584 cells/μL. As such, this trial included some patients with blood eosinophil counts <400 cells/μL, unlike the four other trials which had ≥400 cells/μL.

Trial Res-5-0010 was a 15-week randomised, double-blind placebo-controlled trial evaluating the efficacy and safety of reslizumab (3.0 mg/kg) in patients aged 18-75 years with poorly

controlled eosinophilic asthma.[22] Although this RCT met the company's inclusion criteria, it was excluded from further discussion in the CS as it was a 'phase II proof of concept study that informed the phase II/ clinical programme'. No details of the trial (i.e. baseline characteristics of the population, methods) or the company's critique of it are given in the CS. Despite performing no quality assessment of the RCT or presenting any trial information, the company included data from this trial in their direct comparison meta-analysis and ITC. In response to a request from the ERG via NICE, the company provided a quality assessment for Res-5-0010 (clarification A9). An overview of the five RCTs is presented in (Table 4). Given that details of Res-5-0010 are not provided in the CS, we have obtained these from the trial publication.[22]

All the included RCTs were multi-centre trials, but none included UK patients. All five RCTs were sponsored by the company.

The CS also provides pooled adverse events (AE) data based on all five trials (3082, 3083, 3081, 3084 and Res-5-0010). This was used during the application for EU marketing authorisation for the evaluation of safety evidence. In this cohort (named 'Cohort 3' in CS section 4.12.3.1), 1861 out of the 1870 patients randomised received at least one dose of study drug (safety analysis set) (see section 3.1.6 below for analysis population definitions), but only 79% of these patients (1463/1861) had eosinophil counts ≥400 cells/μL at screening or baseline. While a total of 1131 patients were treated with reslizumab, 103 of these patients were treated with the lower dose of 0.3 mg/kg reslizumab (730 patients were treated with placebo). These data are not considered in detail in the current report since longer-term adverse events data are now available from an open-label extension study (see section 3.1.3.4).

No details of crossovers or dropouts were reported in the reslizumab trials. However, dropouts were reported in the CONSORT diagrams for each trial (CS Figures 3, 4, 35 & [redacted]). Note that the CONSORT flow chart for trial 3084 (CS Figure 35) contains an error, which the company explained in their clarification response (clarification A2). Despite being randomised, fifteen participants are not accounted for in the diagram due to site terminations in the USA. Data for these participants were deemed invalid by the company and therefore excluded from CS Figure 35.

Table 4 Overview of reslizumab RCTs included in the CS

	Trial 3082	Trial 3083	Trial 3081	Trial 3084	Trial Res-5-0010
Trial Date	4/2011 to 3/2014	3/2011 to 4/2014	2/2011 to 9/2013	2/2012 to 8/2013	2/2008 to 1/2010
Number of Patients	489	464	315	496	106
Population	Age 12-75 years with asthma and elevated blood eosinophils (≥ 400/µL) inadequately controlled with medium to high dose ICS		Age 12-75 years with asthma and elevated blood eosinophils (≥ 400/µL) inadequately controlled with medium to high dose ICS	Age 18-65 years with moderate to severe asthma inadequately controlled with medium to high dose ICS	Aged 18-75 years with asthma and eosinophilic airway inflammation (sputum eosinophils ≥3%) poorly controlled with ICS
Design	52 weeks double-blind, placebo-controlled RCT (1:1) Follow-up visit 90 days after the end of the 52 week period or early withdrawal[19]		16 weeks, double-blind, placebo-controlled RCT (1:1:1)	16 weeks double-blind, placebo-controlled, RCT (4:1)	15 weeks double-blind, placebo-controlled RCT (1:1)
Number of centres and countries	102 centres in 17 countries (Australia, Belgium, Chile, Columbia, Czech Republic, Denmark, Hungary, Israel, Malaysia, New Zealand, Philippines, Poland, Russia, South Africa, Sweden, Thailand and USA)	82 centres in 15 countries (Argentina, Brazil, Canada, France, Germany, Greece, Republic of Korea, Mexico, Peru, Romania, Russia, Slovak Republic, Taiwan, Ukraine and USA)	68 centres in 12 countries (Argentina, Belgium, Brazil, Canada, Colombia, Hungary, Israel, Mexico, Netherlands, Poland, Sweden and USA)	103 centres in the USA	25 centres in the USA and Canada
Treatment and comparator	Reslizumab (once every 4 weeks over 52 weeks, total of 13 doses) 3.0 mg/kg (n=245) or placebo (n=244)	Reslizumab (once every 4 weeks over 52 weeks, total of 13 doses) 3.0 mg/kg (n=232) or placebo (n=232)	Reslizumab (once every 4 weeks for 16 weeks, total of 4 doses) 0.3 mg/kg (n=104) or 3.0 mg/kg (n=106), or placebo n=105)	Reslizumab (once every 4 weeks, total of 4 doses) 3.0 mg/kg (n=398) or placebo (n=98)	Reslizumab (once every 4 weeks, total of 4 doses) at 3.0 mg/kg (n=53) or placebo (n=53) (Infusions of reslizumab at baseline, and weeks 4, 8 and 12[21])
Stratification Factors	- Maintenance oral corticosteroid use (Yes or No) - Region (US or other)		- Age (12-17 or ≥18 years) - Asthma exacerbations within the past 12 months (Yes or No)	Asthma exacerbations within the past 12 months (Yes or No)	ACQ score ≤2 or >2

Table 4 - continued

	Trial 3082	Trial 3083	Trial 3081	Trial 3084	Trial Res-5-0010
Primary outcome	Clinical asthma exacerbations (CAE) during the 52-week treatment period (secondary analysis: frequency of CAEs requiring oral or systemic corticosteroids for ≥3 days and frequency of asthma exacerbations resulting in hospitalisation or a visit to the emergency room)		Lung function (FEV_1: overall change from baseline over 16 weeks of treatment) (secondary analysis as above for subgroup: patients in the FAS with % predicted FEV_1, ≤85% at baseline)	Lung function (FEV_1: change from baseline to Week 16) (secondary analysis as above for subgroup: patients in the FAS with % predicted FEV_1 ≤85% at baseline[21])	Change in ACQ score from baseline to week 16
Secondary/ tertiary outcomes ***~~Exploratory variables~~***	Change from baseline to week 16 and/or overall change from baseline: FEV_1 and blood eosinophil count. Change from baseline to week 16: AQLQ. Overall change from baseline: ACQ, ASUI, SABA use. Time to first CAE Other efficacy outcomes: Change from baseline to planned time points in: lung function (FEV_1, FVC, $FEF_{25\%-75\%}$, % predicted FEV_1), ASUI, ACQ, SABA use, AQLQ, and blood eosinophil count		Change from baseline to planned time points in: lung function (FEV_1, FVC, $FEF_{25-75\%}$ and % predicted FEV_1); ACQ, ASUI, SABA use, AQLQ, and blood eosinophil count. ***~~Sputum eosinophils, biomarkers (blood samples to assess changes in eosinophil cationic protein, eosinophil-derived neurotoxin and eosinophilic peroxidase), nasal polyps (not all centres)~~***	Change from baseline to planned time points in: lung function (FEV_1, % predicted FEV_1, FVC, $FEF_{25\%-75\%}$), SABA use, blood eosinophil count, ACQ	Change from baseline to week 16 or early withdrawal: lung function (FEV_1, % predicted FEV_1, FVC and $FEV_{25-75\%}$), eosinophil (induced sputum and blood) and, % of patients with CAE

Exploratory variables	Sputum eosinophils, biomarkers (not all centres), peak expiratory flow rate, Fibulin-1, nasal polyps (not all centres) and immunoglobulin E	Sputum eosinophils, biomarkers (not all centres) and peak expiratory flow rate	*Sputum eosinophils, biomarkers (blood samples to assess changes in eosinophil cationic protein, eosinophil-derived neurotoxin and eosinophilic peroxidase), nasal polyps (not all centres)*		

Information based on Table 13 (Section 4.3.1) and Table 52 (Section 4.7.4) of the CS.
ACQ, Asthma Control Questionnaire; ASUI, Asthma Symptom Utility Index; AQLQ, Asthma Quality of Life Questionnaire; CAE, clinical asthma exacerbation; FEV_1, forced expiratory volume in one second; ICS, inhaled corticosteroids; SABA, short-acting beta-agonist.

3.1.3.1 Similarity of baseline characteristics within trials

Patients participating in the trials were predominantly of white race, with a higher proportion of women. A clinical advisor to the ERG commented that gender imbalances are common in severe asthma, with large international cohort studies showing that 60-70% of those affected are females. In trials 3082, 3083 and 3081, treatment arms within the trials are reported in the CS to be well balanced with regard to age, body weight, height, and body mass index, and the ERG agrees (see Table 5). For trial 3084 the CS describes the patient characteristics as well balanced (CS Table 53), *highlighting an* exception that the proportion of females in the reslizumab arm (66%) was slightly higher than in the placebo arm (55%). The CS does not report or discuss the patients' characteristics at baseline in trial Res-5-0010, but we note from the trial publication that mean disease duration was around three years less for the reslizumab treatment arm compared to the placebo treatment arm in Res-5-0010. Note that not all reported baseline measures were based on the total number of patients in the treatment arms of the trials.

Exacerbations

Where reported (in trials 3082, 3083 and 3081), the mean numbers of exacerbations experienced by patients in the previous 12 months were similar between treatment arms. The largest difference was in trial 3081, where 3% more patients in the reslizumab treatment arm experienced exacerbations in the previous 12 months (reslizumab 57%; placebo 54%). Other measures of exacerbations were similar between treatment arms in the RCTs where reported.

Lung function

Baseline lung function measures were generally similar between treatment arms in the trials, with some exceptions. However, some variation is to be expected in a heterogeneous disease. As shown in Table 5, differences in FEV1 between reslizumab and placebo arms ranged from 0.03 L to 0.13 L (largest in trial 3083); differences in % predicted FEV1 ranged from 0.7% to 3.3% (largest in Res-5-0010); differences in FVC ranged from 0.06 to 0.3 L (largest in Res-5-0010); and differences in $FEF_{25-75\%}$ ranged from 0.07 L/sec to 0.35 L/sec (largest in Res-5-0010).

Medication use

The mean daily dose of ICS varied between the treatment arms (not reported in trial 3084). It was lower in the reslizumab arm in trial 3082 (reslizumab 824.1 µg; placebo 847.7 µg) but lower in the placebo arms of trial 3081 (reslizumab 856.0 µg; placebo 756.9 µg) and trial 3083 (reslizumab 813.5 µg vs 756.9 µg placebo). Trial Res-5-0010 only reported that patients' ICS use was equivalent to ≥440 mg of fluticasone twice daily. There were no imbalances in OCS use between treatment arms in the two trials which reported it (see Table 5).

Three trials reported the mean proportion of patients using SABA in the past 3 days, and in two of these the proportion was higher in the placebo arm: trial 3082 (reslizumab 69%; placebo 77%), and trial 3081 (reslizumab 78%; placebo 81%). Clinical experts advising the ERG suggested that these differences in ICS and SABA use would not be clinically important.

3.1.3.2 Similarity of baseline characteristics across trials

The CS describes patient demographics at baseline as being generally similar across trials 3082, 3083 and 3081, but does not compare these with the baseline characteristics of trial 3084 (CS Table 53). The CS does not report or discuss any baseline characteristics of trial Res-5-0010 and so we have consulted the trial publication for information (where reported). The ERG agrees that in many respects the baseline characteristics of the five trials are similar. However, there are some differences which we have summarised here. Note that not all baseline characteristics were reported in all of the trials (these discrepancies are indicated by asterisks in Table 5).

Time since diagnosis

The trials differed in patients' mean years since diagnosis, which ranged from 18.5 years (trial 3083) to 26.0 years (trial 3084).

Blood eosinophils

Mean blood eosinophil count was considerably lower in trial 3084 compared to the other trials (mean 280 cells/µL instead of ≥400 cells/µL), as would be expected from a study that recruited patients with moderate to severe eosinophilic asthma that was poorly controlled with ICSs.

OCS use

There were considerable differences in OCS use. One study did not allow OCS use (trial 3081, two failed to report this outcome (trials 3084 and Res-5-0010), and for the two remaining trials this ranged from 12% (trial 8083) to 19% (trial 3082) of the trial population. SABA use was similar for the three trials which reported it (trials 3082, 3083 and 3081), while mean daily SABA puffs varied from 2.0 (trial 3084) to 2.8 (trial 3083).

Exacerbations

Three trials reported the number and proportion of patients who had exacerbations in the previous 12 months. The proportion was markedly lower in trial 3081 (range 54% to 57% across the two arms) than in trials 3082 and 3083 (range 99% to 100% across the arms). Patients were required to have had ≥1 asthma exacerbation in the 12 months prior to screening to be eligible for trials 3082 and 3083, but 99% and 99.5% of patients respectively met this criterion.

Asthma control

ACQ scores at baseline ranged from 2.47 (trial 3081) to 2.8 (Res-5-0010), indicating that the patients had a similar degree of asthma control across all five trials (on the ACQ scale 0=totally controlled and 6=severely uncontrolled). The ACQ has an accepted cut-point where ≥1.5 is indicative of uncontrolled asthma[23] (see section 3.1.5). Based on this cut-point, patients in all the trials would be classed as having uncontrolled asthma at baseline.

HRQoL

AQLQ scores at baseline ranged from 4.16 (trial 3082) to 4.37 (trial 3081), indicating that patients had a similar degree of impairment in HRQol across the trials (on the AQLQ scale 1=severely impaired and 7 =not impaired). Scores on the ASUI ranged from 0.61 (trial 3082) to 0.67 (trial 3081), indicating patients had a similar degree of symptom problems across the trials (on the ASUI scale 0=greatest symptom problems, 1=least symptom problems). Note that baseline AQLQ and ASUI were not reported in trials 3084 or Res-5-0010.

Lung function

Baseline lung function was reported in five trials and varied slightly across the trials. FEV1 was slightly worse in trial 3082 (1.9 L) than in the other four trials (range 2.00 L to 2.20 L) and % predicted FEV1 showed a similar pattern, being slightly lower in trial 3082 (63.6% and 65.0% in the two arms) than in the other four trials (range 66.1% to 71.1%). Baseline FVC was more

variable (range 2.96 L to 3.43 L), with some differences within trials being as large as those between trials.

Sex, race

As shown in Table 5, there were more female than male patients in all of the RCTs, ranging from 55% (Res-5-0010) to 66% (trials 3082 and 3084). Patients were predominantly white in all the trials that reported race, ranging from 65% (trial 3084) to 85% (trial 3081).

Other characteristics

Where reported, the trials were similar in terms of patients' mean age (range 43.6 years in trial 3081 to 47.0 years in trial 3083), mean weight (range 74.3 kg in trial 3083 to 76.9 kg in trial 3082) and mean height (range 165.0 cm in trial 3082 to 168.7 cm in trial 3084).

Table 5 Baseline characteristics of the reslizumab trials included in the CS

Baseline characteristic	Trial 3082 (CS Tables 17-18)		Trial 3083 (CS Tables 17-18)		Trial 3081 (CS Tables 17-18)		Trial 3084 (CS Tables 53-55)		Trial Res-5-0010 (Castro et al.[22])	
	RES n=245	**Placebo n=244**	**RES n=232**	**Placebo n=232**	**RES n=106**	**Placebo n=105**	**RES n=398**	**Placebo n=98**	**RES n=53**	**Placebo n=53**
Age, mean (SD) years	46.6 (13.82)	46.7 (14.83)	46.4 (13.79)	47.5 (13.75)	43.0 (14.41)	44.2 (14.89)	44.9 (12.00)	45.1 (13.38)	44.9 (13.94)	45.8 (11.74)
Gender M:F, %	42:58	34:66	38:62	35:65	42:58	41:59	34:66	45:55	36:64	45:55
Race, n (%)										
White	173 (71)	182 (75)	168 (72)	169 (73)	90 (85)	85 (81)	260 (65)	73 (74)	NR	NR
Black	14 (6)	20 (8)	6 (3)	4 (2)	5 (5)	7 (7)	113 (28)	21 (21)	NR	NR
Asian	50 (20)	33 (14)	16 (7)	21 (9)	2 (2)	0	0	0	NR	NR
American Indian/ Alaskan Native	0	0	7 (3)	4 (2)	0	1 (<1)	0	0	NR	NR
Pacific Islander	1 (<1)	0	0	1 (<1)	0	1 (<1)	0	0	NR	NR
Other	7 (3)	9 (4)	35 (15)	33 (14)	9 (8)	11 (10)	25 (6)	4 (4)	NR	NR
Ethnicity, n (%)										
Hispanic/Latino	28 (11)	21 (9)	54 (23)	53 (23)	31 (29)	29 (28)	NR	NR	NR	NR
Non-Hispanic/ non-Latino	216 (88)	223 (91)	177 (76)	178 (77)	75 (71)	74 (70)	NR	NR	NR	NR
Unknown	1 (<1)	0	1 (<1)	1 (<1)	0	2 (2)	NR	NR	NR	NR
Weight, mean (SD) kg	75.6 (19.05)	76.5 (18.71)	74.7 (15.72)	73.9 (15.93)	75.7 (20.30)	77.0 (20.10)	NR	NR	NR	NR
Height, mean (SD) cm (n/N)	164.9 (10.42)	165.0 (9.74)*	166.4 (9.56)	165.2 (9.81)	165.9 (10.24)	166.4 (10.93)	167.7 (10.35)	169.7 (10.25)	NR	NR
BMI, mean (SD) kg/m^2	27.7 (6.26)	28.0 (6.16)*	27.0 (5.26)	27.0 (5.05)	27.4 (6.87)	27.7 (6.01)	32.3 (8.69)	31.6 (6.66)	NR	NR
Years since diagnosis, mean (SD) (n/N)	19.7 (15.19)*	18.8 (14.2)*	18.2 (14.43)	18.7 (13.28)*	20.4 (15.64)* (n=100/106)	20.7 (14.49)	26.2 (15.69)* (n=390/398)	25.8 (16.75)* (n=93/98)	23.3 (11.38)	26.1 (16.06)

Table 5 - continued

Baseline characteristic	Trial 3082 (CS Tables 17-18)		Trial 3083 (CS Tables 17-18)		Trial 3081 (CS Tables 17-18)		Trial 3084 (CS Tables 53-55)		Trial Res-5-0010 (Castro et al.[22])	
	RES n=245	Placebo n=244	RES n=232	Placebo n=232	RES n=106	Placebo n=105	RES n=398	Placebo n=98	RES n=53	Placebo n=53
Patients with exacerbations in last 12 months,[a] n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No. of exacerbations in previous 12 months, mean (SD) (n/N)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Months since last exacerbation, mean (SD) (n/N)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of allergy and/or nasal polyps, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic sinusitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atopic dermatitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aspirin sensitivity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allergic rhinitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allergy shots	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eosinophilic oesophagitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eosinophilic gastroenteritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasal polyps	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 5 - continued

Baseline characteristic	Trial 3082 (CS Tables 17-18)		Trial 3083 (CS Tables 17-18)		Trial 3081 (CS Tables 17-18)		Trial 3084 (CS Tables 53-55)		Trial Res-5-0010 (Castro et al.[22])	
	RES n=245	**Placebo n=244**	**RES n=232**	**Placebo n=232**	**RES n=106**	**Placebo n=105**	**RES n=398**	**Placebo n=98**	**RES n=53**	**Placebo n=53**
Airway reversibility, mean (SD)%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FEV_1, mean (SD) L (n/N)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% predicted FEV_1, mean (SD) (n/N)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FVC, mean (SD) L (n/N)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
$FEF_{25–75\%}$, mean (SD) L/second (n/N)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACQ, mean (SD) overall score	2.657 (0.8541)	2.763 (0.8782)	2.570 (0.89)	2.605 (0.79)	2.590 (0.9108)	2.471 (0.8301)	2.56 (0.70)*	2.57 (0.69)*	2.8 (0.79)	2.5 (0.73)
AQLQ, mean (SD) overall score (n/N)	4.303 (1.12	4.159 (1.0883)*	4.352 (1.0220)*	4.223 (1.0794)*	4.175 (1.2297)*	4.374 (1.2047)	NR	NR	NR	NR
ASUI, mean (SD) overall score (n/N)	0.633 (0.1938)*	0.613 (0.2029)*	0.664 (0.2005)*	0.649 (0.1919)*	0.655 (0.1945)	0.674 (0.1897)	NR	NR	NR	NR
Blood eosinophil count mean (SD) cells/µL (n/N)	696 [b] (767.7)	624 [b] (590.3)	610 [b] (411.5)	688 [b] (682.4)	592 [b] (387.8)	601 [b] (433.1)	280 (245.4)*	279 (221.3)*	Median 500 (min 100, max 1500)	Median 500 (min 0, max 1200)

Table 5 - continued

Baseline characteristic	Trial 3082 (CS Tables 17-18)		Trial 3083 (CS Tables 17-18)		Trial 3081 (CS Tables 17-18)		Trial 3084 (CS Tables 53-55)		Trial Res-5-0010 (Castro et al.[22])	
	RES n=245	**Placebo n=244**	**RES n=232**	**Placebo n=232**	**RES n=106**	**Placebo n=105**	**RES n=398**	**Placebo n=98**	**RES n=53**	**Placebo n=53**
Total daily ICS dose, mean (SD) µg (n/N)	824.1 (380.28)* (n=240/245)	847.7 (442.13)*	856.0 (588.40)*	756.9 (274.23)*	813.5 (452.74)*	756.7 (370.59)	NR	NR	Received ICS equivalent to ≥440 mg of fluticasone BID	
OCS, n (%)	46 (19)	46 (19)	27 (12)	27 (12)	0	0	NR	NR	NR[c]	NR[c]
SABA use past 3 days, n (%) (n/N)	170 (69)	188 (77)	182 (78)	181 (78)	78 (74)	81 (77)	NR	NR	NR	NR
Daily average no. of puffs,[d] mean (SD) (n/N)	2.4 (2.82)*	2.7 (3.18)*	2.9 (2.82)* (n=204/232)	2.7 (2.41)* (n=201/232)	2.2 (2.56)	2.3 (2.20)*	1.9 (1.84)* (n=392/398)	2.0 (1.82)*	NR	NR

ACQ, Asthma Control Questionnaire; ASUI, Asthma Symptom Utility Index; AQLQ, Asthma Quality of Life Questionnaire; BID = twice daily; $FEF_{25–75\%}$, forced expiratory flow at 25–75% forced vital capacity; FEV^1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; L, litre; NR, not reported; RES: reslizumab; SABA, short-acting beta-agonist; SD, standard deviation.

*Asterisks indicate data were for fewer patients than the number randomised; where differences were ≥5 patients these are indicated in brackets

[a] Definitions of asthma exacerbations. 3082 and 3083: investigator-determined exacerbations requiring oral, intramuscular or intravenous corticosteroids for ≥3 days in the 12 months prior to screening. 3081: any of the following: 1) A ≥20% reduction in FEV1, 2) Hospitalisation because of asthma, 3) Emergency treatment because of asthma, or 4) Use of prednisone or systemic corticosteroids for ≥3 days. 3084: any of the following: 1) a ≥20% reduction in FEV1, 2) hospitalisation because of asthma, 3) emergency treatment because of asthma, or 4) use of prednisone or systemic corticosteroids for ≥3 days (case report form data).

[b] Includes some patients with a value below 400/µL, as patients were required to have a blood eosinophil count ≥400/µL at least once during the screening period, but this value did not necessarily occur at baseline.

[c] Reported number/percentage of patients receiving long-acting beta-agonists (Reslizumab 94%, Placebo 96%), Leukotriene antagonists (Reslizumab 17%, Placebo 32.1%) and
Cromolyn sodium (both groups 1.9%)

[d] Based on patient-reported number of puffs over the past 3 days.

3.1.3.3 Ongoing trials

The CS states (section 4.14) that there are "no completed or ongoing company-sponsored studies from which new evidence for reslizumab in patients with asthma and elevated blood eosinophils will become available in the next 12 months", but it does not mention any trials not sponsored by the company that may complete within the next 12 months. As mentioned above (section 3.1.1), the ERG did not identify any relevant ongoing studies of reslizumab. In response to a query from the ERG via NICE, the company provided a list of relevant ongoing studies, regardless of the evidence becoming available in the next 12 months (clarification A13).

3.1.3.4 Non-randomised studies

The CS cites one open-label extension study, 3085, for supporting evidence on safety. Patients entered study 3085 after participating in trials 3082, 3083 and 3081 (CS Table 87). The data from study 3085 reported in the CS are from a clinical study report, with some data marked AiC. A total of [redacted] patients were enrolled, with [redacted] receiving at least one dose of reslizumab. [redacted] percent of patients [redacted] received reslizumab for the first time, having received placebo in the preceding studies. A total of [redacted] patients completed the study (i.e. the 104-week treatment period and the 90-day follow-up period); the main reason for withdrawal [redacted] was [redacted].

3.1.4 Description and critique of the approach to validity assessment

The CS provides a quality assessment for four of the included RCTs (3082, 3083, 3018 and 3014) using standard criteria as recommended by NICE (CS section 4.6; CS Table 19 and CS Appendix 3). However, the CS does not report quality assessment for the fifth RCT which was included in the submission (Res-5-0010) and therefore the ERG requested this information from the company via NICE (clarification A9). The ERG's critique of the company's quality assessment for these five RCTs is shown in Table 6.

Table 6 Company and ERG assessments of trial quality

Quality assessment question		Trial 3082	Trial 3083	Trial 3081	Trial 3084	Trial Res-5-0010
1. Was randomisation carried out appropriately?	CS:	Yes	Yes	Yes	Yes	Yes[a]
	ERG:	Yes	Yes	Yes	Yes	Yes
Comments: none						
2. Was concealment of treatment allocation adequate?	CS:	Yes	Yes	Yes	Yes	Yes[a]
	ERG:	Yes	Yes	Yes	Yes	Yes
Comments: The ERG judgement takes into account additional information which was provided by the company on request via NICE (clarification A11)						
3. Were groups similar at outset in terms of prognostic factors?	CS:	Yes	Yes	Yes	Yes	Yes[a]
	ERG:	Yes	Yes	Yes	Yes	Yes
Comments: NB in study 3081, 9% more patients in the placebo group than reslizumab 3mg group had chronic sinusitis. In study 3084 placebo group had 11% more males/fewer females than the reslizumab 3mg group. NB for study 3084 the CS (Table 53) does not report all available baseline characteristics; the ERG has checked further characteristics as reported in CSR Tables 7 and 8. None of the baseline differences the ERG identified are likely to impact study outcomes.						
4. Were care providers, participants and outcome assessors blind to treatment allocation?	CS:	Yes	Yes	Yes	Yes	Yes[a]
	ERG:	Yes	Yes	Yes	Yes	Yes
Comments: none						
5. Were there any unexpected imbalances in drop-outs between groups?	CS:	No	No	No	No	Yes[a]
	ERG:	No	No	No	No	Yes
Comments: NB across the five RCTs the dropout rate per arm ranged from 6% to 19% but reasons were balanced across groups within each RCT, except for Res-5-0010 where there was an imbalance in dropouts (6% reslizumab arm, 17% placebo arm), mainly due to lack of efficacy.						
6. Is there any evidence that authors measured more outcomes than they reported?	CS:	No	No	No	No	No[a]
	ERG:	No	No	No	No	No
Comments: none						
7**. Did the trial include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?**	CS:	Yes	Yes	Yes	Yes	Yes[a]
	ERG:	ITT: No; Missing data method: no	ITT: No; Missing data method: no	ITT: No; Missing data method: no	ITT: No; Missing data method: no	ITT: No; Missing data method: yes
Comments: Although sensitivity analyses and data imputation methods are reported in the CS for trials 3082, 3083, 3081 and 3084, these would be applicable specifically if the analysis is based on the ITT population or, where defined, the FAS. In contrast, for the outcome analyses reported in the CS, the sample sizes given are smaller than the ITT population and, where defined, also smaller than the FAS (i.e. missing data are excluded from analysis). Reasons for missing data are not reported in the CS.						

NR: not reported

[a] Information provided in company's clarification response to the ERG (clarification A9)

Overall, we agree with the company's assessments of the trial quality, with the exception that we considered that in all trials analysis population was not an ITT population, since for most of the outcomes analysed in the CS the sample sizes reported are smaller than the number randomised and, where defined, also smaller than the FAS.

In addition to the quality assessments of reslizumab RCTs reported in the CS, the ITC Report[16] provided by the company includes a summary of the company's quality assessments for the five reslizumab RCTs and 16 omalizumab RCTs that were identified as potentially relevant for the ITC analysis (ITC Report Appendix 10), meaning that quality assessment for the reslizumab RCTs is duplicated. The quality assessment for the reslizumab RCTs in the ITC Report is nearly identical to that provided in the CS, but there is a discrepancy for the question about ITT analyses: this was answered "no" for RCTs 3082, 3083, 3018 and 3984 in ITC Report but was answered "yes" for these RCTs the CS. As shown in Table 6, we concur with the company's judgement provided in the ~~*CS version*~~ *ITC Report*.

Another discrepancy which came to light after the ERG had received the company's quality assessment of RCT Res-5-0010 (clarification A9) is that the company's answer to the question about imbalances in dropouts was "no" in the ITC Report but "yes" in the clarification response. As shown in Table 6, we concur with the company's judgement provided in the clarification response.

In addition to the quality assessment of the RCTs, the company conducted a quality assessment for the non-randomised (single arm) open label extension study 3085 which was primarily a study of reslizumab safety. The quality assessment for study 3085 (CS Appendix 5) was based on a checklist but the CS does not identify the source.

3.1.5 Description and critique of the company's outcome selection

The outcomes specified in the CS are asthma control, rates of clinically significant asthma exacerbations, lung function, adverse events, and HRQoL. These are consistent with the NICE scope. However, the company has not reported patient and clinician evaluation of response, mortality, or time to discontinuation, which are specified as outcomes in the NICE scope, and the CS does not explain why these outcomes are missing. We have checked the clinical study reports for trials 3082, 3083, 3081 and 3084 and the publication for Res-5-0010 and confirm that none of the included trials reported patient and clinician evaluation of response or time to discontinuation. Across the five trials only one death occurred, and this was in the placebo arm of trial 3082.

In addition to the outcomes listed in the NICE scope, the CS reports use of short-acting beta agonists (SABA) and also blood eosinophil concentrations which provide supporting clinical information on medication use and the degree of eosinophilic inflammation respectively.

In summary, the outcomes presented in the CS are appropriate for the evaluation of severe eosinophilic asthma and, where available, are consistent with the NICE scope:

Asthma control

Asthma control was assessed using the change from baseline in the Asthma Control Questionnaire (ACQ) score in five trials (3082, 3083, 3011, 3084, Res-5-0010). The ACQ is a validated and widely used instrument which has seven questions, each with a possible score ranging from 0–6. The total score is the mean of all responses which gives a score ranging from 0 (totally controlled asthma) to 6 (severely uncontrolled asthma). Six of the questions are self-assessments; one is the result of the patient's % predicted FEV_1 measurement. The minimum clinically important difference for the ACQ is regarded as a change of score ≥0.5.[23] The seven-question version of the ACQ is considered useful in discriminating between 'well-controlled' and 'not well-controlled' asthma. Juniper and colleagues[23] demonstrated that to be confident that a patient has well-controlled asthma, the optimal cut-point on the ACQ is 0.75 (negative predictive value=0.85); whilst to be confident that the patient has inadequately controlled asthma, the optimal cut-point on the ACQ is 1.50 (positive predictive value=0.88).

In addition to analysing changes in ACQ scores, the CS also reports an 'ACQ responder analysis', referring to the proportion of patients in the reslizumab and placebo groups who achieved a change in ACQ score of at least 0.5.

Exacerbations

The NICE scope specifies "Incidence of clinically significant exacerbations, including those which require unscheduled contact with healthcare professionals or hospitalisation". Exacerbations were reported by trials 3082, 3083, 3081 and Res-5-0010. Trials 3082 and 3083 use the term "clinical asthma exacerbations" (CAE) which appears consistent with the NICE scope. The definitions reported in the trials are as follows:

Trials 3082 and 3083: An exacerbation event was defined as a clinical asthma exacerbation (CAE) if the patient met either or both of the following criteria:

(1) Use of systemic (oral, intravenous or muscular), or an increase in the use of inhaled, corticosteroid treatment for ≥3 days. For patients already being treated with systemic or inhaled corticosteroids, the dose of corticosteroids needed to be increased ≥2 fold for at least 3 days.

(2) Asthma-related emergency treatment including at least one of the following:

- An unscheduled visit to the physician's office for nebuliser treatment or other urgent treatment to prevent worsening of asthma symptoms.
- A visit to the emergency room for asthma-related treatment.
- An asthma-related hospitalisation.

The above criteria had to be corroborated with at least one other measurement to indicate worsening in the clinical signs and symptoms of asthma, as follows:

- Decrease in FEV1 by ≥20% from baseline;
- Decrease in PEFR by ≥30% from baseline on two consecutive days; or
- Worsening of symptoms or other clinical signs per physician evaluation of the event.

The investigator recorded essential elements of a CAE (i.e. the type of medical intervention and/or a decrease in lung function) in the electronic case report form; asthma worsening events recorded in the form are referred to as investigator-determined CAEs.

Trial Res-05-0010: A clinical asthma exacerbation was defined as (1) a 20% or more decrease from baseline in FEV1; or (2) worsening of asthma requiring emergency treatment, hospital admission, or three or more days of oral corticosteroid treatment. Patients with exacerbations were treated according to the investigator's discretion.

Trial 3081: Asthma exacerbations or events of worsening asthma were not used as a measure of efficacy in trial 3081; instead these events were recorded as an adverse event and coded as an asthma exacerbation, defined by one of the following: 1) a ≥20% reduction in FEV1, 2) hospitalisation because of asthma, 3) emergency treatment because of asthma, or 4) use of prednisone or systemic corticosteroids for ≥3 days. However, the company has not included trial 3081 in any analyses of exacerbations.

Lung function

The CS reports analyses of changes from baseline in the following lung function outcomes measured by spirometry:

- FEV_1 (trials 3082, 3083, 3011, 3084, Res-5-0010): The volume of air expelled in the first second of a forced expiration.
- % predicted FEV_1 (trials 3082, 3083, 3011, 3084, Res-5-0010): The ratio of the volume of air expired in the first second of a forced expiration to the patient's predicted FEV.
- FVC (trials 3082, 3083, 3011, 3084, Res-5-0010): The volume of air that can be forcibly blown out after full inspiration.
- $FEF_{25–75\%}$ (trials 3081, 3084): The forced expiratory flow at 25–75% of the FVC.
- PEFR (trials 3082, 3083, 3081): The greatest rate of airflow that can be obtained during a forced exhalation.

Expert advice to the ERG suggests that $FEF_{25–75\%}$ can be quite variable and is not routinely used in clinical practice; however, we have included this outcome in the present report for completeness. The CS only reports PEFR for small subgroups of patients and for this reason we have not included PEFR in the present report.

HRQoL

Three reslizumab trials used the change from baseline in the Asthma Quality of Life Questionnaire[24] (AQLQ) score as their primary measure of HRQoL (trials 3082, 3083, 3081). The AQLQ is a validated and widely-used instrument which has 32 questions in 4 domains (symptoms, activity limitation, emotional function, and environmental stimuli). Patients were asked to recall their experiences during the last 2 weeks. The AQLQ score ranges from 1 indicating severe impairment to 7 indicating no impairment. The minimum clinically important difference for AQLQ change is considered to be ≥0.5.[25] A clinical expert advising the ERG commented that whilst the AQLQ is validated and widely used for assessing

HRQoL in patients with asthma, it has not been specifically validated in patients with severe asthma.

In addition to analysing changes in AQLQ scores, the CS also reports an 'AQLQ responder analysis', referring to the proportion of patients in the reslizumab and placebo groups who achieved a change in AQLQ score of at least 0.5.

The same trials also reported scores for the Asthma Symptoms Utility Index (ASUI), another validated and widely used instrument, although the company did not include these in any analyses. The ASUI has 11 items to assess the frequency and severity of asthma symptoms and side effects, weighted by patient preferences. The ASUI score ranges from 0 to 1, with lower scores indicating greater asthma symptom problems.

SABA use

SABA use was assessed in trials 3082, 3083, 3081 and 3084. Patients were asked to recall whether SABAs were used within 3 days of the scheduled visit and, if so, how many puffs were used.

Blood eosinophil counts

Blood eosinophil counts were assessed in trials 3082, 3083, 3011, 3084 and Res-5-0010). This was measured using a standard complete blood count with differential blood test.

3.1.6 Description and critique of the company's approach to trial statistics

Analysis populations in the clinical trials

The company's assessment of trial quality (CS Table 19) states that trials 3082, 3083, 3081 and 3084 employed an intent-to-treat (ITT) analysis (i.e. in which all randomised patients were analysed), although the CS when referring to these trials does not explicitly mention ITT but instead refers to the 'randomised set'. Other populations in the trials as referred to in the CS are:

- 'full analysis set' (FAS): defined as the number of trial participants who were treated with at least one dose of study drug (trials 3082, 3083, 3081)
- 'safety analysis set' (SAS): defined the same as the FAS

The relationship between the analysis populations in each trial is summarised in Table 7.

For trial 3084 the CS does not mention FAS but instead refers to 'patients evaluable for efficacy'. The clinical study report for trial 3084 does define FAS in the same way as for the other trials but the numbers of patients are slightly different to those described in the CS as 'evaluable for efficacy'.

Table 7 Analysis populations in the trials of reslizumab

Trial	Arm	Number randomised	Full analysis set (number treated with ≥1 dose of study drug)	Evaluable for safety
3082	Reslizumab	245	245 (100%)	245 (100%)
	Placebo	244	243 (97%)	243 (>99%)
3083	Reslizumab	232	232 (100%)	232 (100%)
	Placebo	232	232 (100%)	232 (100%)
3081	Reslizumab[a]	106	103 (97%)	103 (97%)
	Placebo	105	105 (100%)	105 (100%)
3084	Reslizumab	398	Not referred to as FAS, but 395 (99%) described as evaluable for efficacy	*395 (99%)*
	Placebo	98	Not referred to as FAS, but 97 (99%) described as evaluable for efficacy	*97 (99%)*
Res-5-0010	Reslizumab	53	Not reported	53 (100%)
	Placebo	53	Not reported	53 (100%)

NR: not reported
[a] excluding a reslizumab 0.3 mg/kg arm which is not relevant to this appraisal

As shown Table 7 (and noted in our critical appraisal of the analysis populations in section 3.1.4), the FAS analysis population was reported to be identical to the randomised set in trial 3083, and differed only marginally from the randomised set in the remaining trials. However, the sample sizes presented in the CS for a number of outcome analyses are considerably smaller than the randomised set or the FAS, indicating that missing data were encountered in some analyses (see results sections 3.3 and 3.4).

For trial 3084 the CS reports outcomes for the total trial population and also for subgroups with blood eosinophil counts <400 and ≥400 per µL. The CS and clinical study report do not explicitly state how many of the randomised population or FAS were in each of these subgroups.

Statistical analysis approaches in the clinical trials

The CS provides a fairly detailed description of the statistical methods used to analyse the primary and secondary outcomes in trials 3082, 3083, 3081 and 3084. An overview of the

statistical approaches employed for the primary outcomes is given in Table 8. Information for trial Res-5-0010 is not given in the CS and we have sourced this from the trial publication.

Table 8 Overview of statistical approaches in the trials of reslizumab

	3082 and 3083 (CS Table 16)	**3081 (CS Table 16)**	**3084 (CS Table 52)**	**Res-5-0010 Castro et al.**[22]
Primary outcome	CAE frequency	Change in FEV1	Change in FEV1	Change in ACQ score
Summary of primary outcome analysis	Negative binomial regression model that included the treatment group and randomisation stratification factors as model factors, and the log of follow-up time excluding the summed duration of CAE events as an offset variable. The ratio (and 95% CI) of CAE rate between treatment groups was estimated from the negative binomial model.	MMRM with treatment, stratification factors, sex, visit, and treatment and visit interaction as fixed effects, height and baseline values as covariates, and patients as a random effect.	Linear regression model to determine whether a relationship exists between baseline blood eosinophils and lung function (FEV1 value at 16 weeks).	ANCOVA adjusting for the stratification factor (ACQ < 2 or ACQ ≥ 2) and baseline values. Least-square means were used to determine the mean differences between reslizumab and placebo.
Statistical power for comparison of reslizumab vs placebo	Approximately 90% power at α=0.05 to detect 33% reduction in CAE rate, assuming CAE rate 1.2 per year for placebo group, allowing for 10% false positive blood eosinophil test at enrolment and 9% dropout per arm	≥90% power at α=0.05 to detect an unspecified difference in change from baseline in FEV1 using 2-sided t-test and MMRM simulation	Not reported	≥90% power at α=0.05 to detect an 0.5 difference in the change from baseline in ACQ score assuming SD=0.76 and 60 patients per arm (actual=53)
Multiple testing accounted for?	Yes. Pre-specified fixed-sequence procedure which was not independent of outcome.		No; stated p-values are nominal	Not reported
Missing data imputation for primary outcome	Missing data were not imputed, as few withdrawals were expected. Sensitivity analysis was conducted to test robustness of the primary model to any missing data.		Missing data were not imputed. Sensitivity analysis was conducted to test robustness of the primary model to any missing data	ITT analysis with last observation carried forward

ACQ: Asthma Control Questionnaire; ANCOVA: analysis of covariance; CAE: clinical asthma exacerbation; MMRM: mixed-effect model for repeated measures

Three trials (3082, 3083, 3081) were adequately statistically powered to detect a specified difference in the primary outcome; one trial (3081) was powered to detect a difference which

was not specified; and the remaining trial (3084) did not report statistical power. Three trials adjusted for multiple testing, one did not adjust for multiple testing (3084), and another did not report this (Res-5-0010). The multiple testing adjustment employed in trials 3082, 3083 and 3081 was based on a fixed-sequence procedure that would be appropriate provided that the most important outcomes are pre-specified as being highest in the order of testing. We note that the specified order of outcome testing (which the CS states is reported in CS Table 13) implicitly ranks asthma control as being of lower importance than lung function and HRQoL in this adjustment approach for multiple testing, although it is not discussed in the CS as to how this should influence the interpretation of statistical significance for each outcome. Four trials (3083, 3082, 3081, 3084) employed sensitivity analyses to assess whether missing data would affect analysis conclusions, whilst Res-5-0010 used a last-observation-carried-forward approach but did not state explicitly to which outcomes and for how many missing data values this was applied.

Although the statistical analysis approaches appear generally reasonable, the company appears to have over-tested some outcomes by employing two different analysis methods in trials 3082, 3083 and 3081 when one analysis would have sufficed. Notably, the CS reports that changes from baseline were analysed “over” 16 (or 52) weeks, and also that they were analysed “to” 16 (or 52) weeks. In response to an ERG query to the company via NICE (clarification A1), the company explained that the “change over” 16 (or 52) weeks can be viewed as the weighted average across the entire period whereas the “change to” 16 (or 52) weeks is the estimate for that specific time-point at week 16 (or 52). The company has not explained why two different measures of change from baseline were needed and not explained which is the preferred analysis, and the methods for analysing the changes from baseline are not reported consistently across all outcomes in the CS. In trial 3084 the change “at” 16 (or 52) weeks is reported and we assume this means the change which the company has referred to as “to” 16 (or 52) weeks in their clarification response. Having results from two analyses of the same outcome increases the possibility of selective reporting of results and also increases the number of multiple comparisons being tested.

Reporting of analyses

Results of the statistical analyses are generally reported clearly in the CS, including the number and proportion of patients where appropriate; point estimates (mean or least squares mean, or median); variance estimates (SD, SE or 95% confidence interval; CI); and effect estimates (hazard ratio, rate ratio or mean difference). Clinically significant differences are reported for the FEV1, ACQ and AQLQ outcomes and these are discussed when interpreting analysis results for these outcomes.

There are some problems with the reporting of analyses, however:

- For binary outcomes the company states in the CS and the ITC Report[16] that results are mean differences when they are actually odds ratios.
- The CS does not explain why, for the majority of the analyses, there are missing data.
- It is unclear from both the CS and clinical study reports whether the ACQ responder analysis was pre-specified or post-hoc.

3.1.7 Description and critique of the company's approach to the evidence synthesis

The CS presents a well-structured evidence synthesis comprising three main parts. These are: a description of the clinical evidence from the five individual RCTs of reslizumab versus placebo (CS section 4.7); a direct comparison meta-analysis in which the results for specified outcomes were pooled across the reslizumab versus placebo RCTs (CS section 4.9); and an indirect treatment comparison (ITC) which estimated pooled outcomes for reslizumab compared to omalizumab based on indirect evidence from combining the reslizumab versus placebo and omalizumab versus placebo RCTs, using placebo (and/or BSC) as a common comparator. The ITC is not reported in the CS but was provided as a separate ITC Report.[16] The clinical effectiveness evidence reported in the CS and the ITC Report is generally presented clearly using tables and graphs and is summarised narratively using concise textual description. We note that results of direct comparison meta-analyses are provided in duplicate, being given in the CS (section 4.9) with the same results also provided in the ITC Report (section 3.2).

3.1.7.1 Description and critique of the direct comparison meta-analysis

The company conducted what the CS describes as direct comparison meta-analysis of "reslizumab versus BSC" (CS ~~page 49~~ section 4.9), where "BSC" refers to the placebo arm of relevant reslizumab RCTs. The ERG believes that the comparison should be more accurately described as reslizumab + BSC versus placebo + BSC. All RCTs included in the meta-analysis evaluated reslizumab 3.0 mg/kg versus placebo, with both arms including BSC. As noted in the CS (section 4.9.1.1), BSC relies on the use of a Personal Asthma Action Plan, the avoidance of environmental or dietary triggers, and the use of

recommended medications (key components of the Personal Asthma Action Plan are provided in CS Appendix 4).

Identification of outcomes and studies

The CS reports a 'feasibility assessment' for each outcome in order to determine which of the RCTs should be included in the direct comparison meta-analysis (Table 10 within CS Appendix 4). The 'feasibility assessment' is merely a list of how many RCTs report each outcome. However, the ERG notes that the 'feasibility assessment' provided is for the ITC instead of the direct comparison meta-analysis and is therefore uninformative.

No clear process is reported for assessing eligibility of the five identified reslizumab RCTs for inclusion in the direct comparison meta-analysis. The CS does present the demographic characteristics of four of the trials[19-21] (CS Tables 17, 18 & 53) and provides quality assessment for these four trials (CS Table 19), but this information is not used to inform study selection for the meta-analysis (CS section 4.9.1.2). Demographic information and quality assessment for the fifth RCT[22] is not provided in the CS. The CS points out that "if trials differ in terms of study design or the trial populations are different in terms of prognostic factors, it can lead to heterogeneity between studies" and it lists nine potential treatment effect modifiers which it states "were assessed across the trials included in the meta-analysis" (CS section 4.9.1.2); however, these effect modifiers were not analysed in the submission.

Outcomes included in direct comparison meta-analysis

Seven outcomes were included in direct comparison meta-analysis (
Table 9). Although the process for deciding why these seven outcomes should be analysed is not clearly explained, they appear to be the outcomes which had the most data available.

The company conducted their meta-analyses for two follow-up assessment times: 16 ± 4 weeks and 52 ± 4 weeks. In response to a clarification request submitted by the ERG via NICE (clarification A12), the company explained that time points were found to vary among the RCTs and an assessment time ±4 weeks was "chosen based on expert opinion". However, of the five RCTs included in direct comparison meta-analysis, only one trial did not report outcomes at 16 and/or 52 weeks: in the RCT by Castro and colleagues[22] the outcome assessment was at 15 instead of 16 weeks.

Table 9 Outcomes included in meta-analyses

Outcomes specified in the NICE scope	Outcomes included in meta-analysis	Numbers of RCTs analysed			
		Direct comparison (RES vs placebo)		Indirect treatment comparison (RES vs OMA)	
		16 week[a]	52 week	16 ± 4 week	52 ± 4 week
Asthma control	Change from baseline in ACQ	5	0[b]	5 RES vs placebo 1 OMA vs placebo 1 OMA vs optimised asthma therapy	0[b]
Incidence of clinically significant exacerbations, including those which require unscheduled contact with healthcare professionals or hospitalisation	Clinically significant exacerbations	3		3 RES vs placebo 2 OMA vs placebo 1 OMA vs optimised asthma therapy	
	Number of patients hospitalised due to exacerbations	1	2	1 RES vs placebo 1 OMA vs placebo	2 RES vs placebo 2 OMA vs BSC
Lung function	Change from baseline in FEV1	5	2	5 RES vs placebo 1 OMA vs placebo 1 OMA vs Control group 1 OMA vs Conventional therapy	2 RES vs placebo 1 OMA vs BSC
Adverse effects (AE) of treatment	Serious AE	3	2	3 RES vs placebo 4 OMA vs placebo	2 RES vs placebo 1 OMA vs placebo 1 OMA vs BSC
	Discontinuations due to AE	3	2	3 RES vs placebo 2 OMA vs placebo	2 RES vs placebo 1 OMA vs placebo
HRQoL	Change from baseline in AQLQ	3	2	4 RES vs placebo 1 OMA vs Control group	2 RES vs placebo 1 OMA vs placebo

ACQ: Asthma Control Questionnaire; AE: adverse events; AQLQ: Asthma Quality of Life Questionnaire; BSC: best standard of care; FEV1: forced expiratory volume in 1 second; OMA: omalizumab; RES: reslizumab.
[a] one study (Castro et al. 2011[22]) had 15 weeks' duration
[b] insufficient data for analysis

Statistical methods for the direct comparison meta-analysis

The CS briefly describes the methods employed for the direct comparison meta-analyses (CS section 4.9.1.3). Apart from exacerbation rates, outcomes were analysed using a standard frequentist method based on the inverse variance weighted approach. For binary outcomes the analysis was based on the number of events and the total number of patients in each treatment arm, whilst for continuous outcomes the analysis was based on absolute differences in mean changes from baseline between the treatment arms. Both fixed and

random effects were estimated. In the random-effects model the between-study variance was estimated using a standard weighted least squares method. For binary outcomes, zero events in one or more study arms would preclude the inverse variance approach and in such cases a Mantel-Haenszel analysis was used instead. The ERG agrees that the frequentist analytical approach employed by the company was appropriate.

Rates of exacerbations were based on time-standardised counts based on person-years so as to account for the different follow-up times in the RCTs and were analysed using a Bayesian framework in WinBUGS. The exacerbation rates were modelled using a Poisson likelihood and log link, where the number of person-years at risk was used rather than the number of patients at risk. The analysis employed non-informative priors and both fixed and random effects were estimated. Model fit was estimated using the deviance information criterion (DIC). The ERG cautions against selecting fixed or random effects models based solely on the DIC since model plausibility is arguably more important than model fit.[26] However, the CS states that, in cases where a random-effects model was selected based on the DIC, the results of the fixed-effects model were reported as a sensitivity analysis. Overall, the Bayesian analysis of exacerbation rates conforms to the NICE DSU guidance on generalised linear modelling for meta-analysis[27] and the ERG agrees that the approach employed by the company was appropriate.

The ERG agrees that the Bayesian analysis of exacerbation rates and frequentist analysis of all other outcomes is reasonable. Frequentist and Bayesian approaches have different pros and cons. The frequentist approach is simple, transparent, and easily reproducible, whilst the Bayesian approach is more complex and less easy to reproduce but well suited to analysing the exacerbation rates data, consistent with NICE DSU guidance.[27] We have no reason to believe that the company's choice of Bayesian versus frequentist analysis approaches would have led to any bias in outcomes.

Missing variance estimates for the frequentist and Bayesian meta-analyses were imputed, as described in the CS (page 136) and the ERG agrees that the company's imputation approach for these parameters was appropriate. In cases where standard deviation data were missing for the mean difference in the change from baseline, the SD was imputed using the mean value of SDs from the arms of the other studies, although the CS does not state which studies provided the imputation sources. An algorithm for obtaining missing standard errors is presented and, for the analysis of exacerbations, also an algorithm for calculating events when only rates were reported. The CS notes which trials these imputations were applied to (e.g. CS Tables 57 & 61).

Missing outcomes data for the individual trials were expected to be few and were dealt with by imputation and sensitivity analysis techniques (see section 3.1.6; Table 8). However, the input data reported in the CS for the company's direct comparison of reslizumab against placebo (results section 3.3) suggest that missing data occurred for the majority of outcomes and were not included in the meta-analysis. Reasons for the missing observations are not explained in the CS.

Statistical heterogeneity in the meta-analyses was estimated using Cochan's Q and the I^2 statistic, with heterogeneity being suspected if Cochran's Q was signficant at a 10% level or if I^2 was greater than 50% (CS page 139). This is a standard and appropriate approach for assessing statistical heterogeneity. However, the CS points out that the Cochran's Q test is limited in its reliability to detect heterogeneity when fewer than five studies are included in a direct comparison meta-analysis. In cases where significant heterogeneity was detected by either of the statistics, forest plots are provided in the CS to illustrate the possible sources of heterogeneity.

Summary of the ERG's critique of the direct comparison meta-analysis

The company's approach for the direct comparison meta-analysis of the effectiveness of reslizumab compared to placebo is generally appropriate. However, there are several limitations:

- The company provides limited information about the comparability of the trials included in meta-analyses (CS section 4.9.1.2), although we have highlighted in section 3.1.3.2 where there are notable differences between the trials.
- The company's 'feasibility assessment' does not clearly explain why some trials are included in the meta-analysis but not others, particularly in relation to trial Res-5-0010 which the CS inconsistently implies is both relevant and not relevant (the ERG requested clarification on this via NICE but the company's response (clarification A9) repeated what is already stated in the CS).
- For most of the outcomes analysed the sample sizes for each trial included in the meta analysis are smaller than the numbers randomised and (where defined) the FAS (section 3.3); no explanation for these missing data is provided in the CS.
- Results of the direct meta-analysis of reslizumab versus placebo do not directly inform the company's economic analysis (section 4).

3.1.7.2 Description and critique of the indirect treatment comparison

No head-to-head comparisons of reslizumab against omalizumab were identified by the company and therefore an ITC was conducted to compare reslizumab against omalizumab, using the placebo and/or BSC arm of each RCT as the common comparator. The ITC is not reported in the CS but was provided by the company as a separate report[16] which hereafter we refer to as the ITC Report.

Assumption underpinning the ITC

As stated in the ITC Report (section 4), omalizumab is indicated in allergic (IgE-mediated) asthma and can only be a relevant comparator to reslizumab for a small overlap population of patients presenting with both allergic and eosinophilic phenotypes of severe asthma. However, detailed information about eosinophil counts at baseline was only available in reslizumab RCTs, not omalizumab RCTs, with one exception. The EXTRA trial of omalizumab versus placebo[28] included a subgroup of patients with both IgE-mediated and eosinophilic asthma (N=414). The company points out, however (ITC Report section 2.3.1), that the subgroup in EXTRA had blood eosinophil concentrations ≥260 per μL, which is not comparable with the definition of elevated blood eosinophils in the reslizumab RCTs (≥400 per μL). The company therefore excluded this subgroup. In order to facilitate the ITC, an important assumption is made that omalizumab has the same treatment effect in the overlap population of patients with both IgE-mediated and eosinophilic asthma as in the overall IgE-mediated asthma population (ITC Report section 2.3.1).

Identification of outcomes and studies

The ITC is based on the 21 RCTs identified in the company's systematic review of clinical effectiveness (i.e. five reslizumab RCTs and 16 omalizumab RCTs). Overall, the approach employed by the company for the ITC was very similar to that described above for the direct comparison meta-analyses. The ITC analysis began with a 'feasibility assessment' (ITC Report Appendix 4) to ascertain which of the 21 identified RCTs should be included in ITC analyses for each outcome. However, the 'feasibility assessment' is merely a list of how many RCTs could potentially provide information for each outcome for each of two specified assessment times, 16 ± 4 weeks and 52 ± 4 weeks, and it does not identify or critique the individual RCTs involved nor mention how many of the trials for each outcome were on each drug. Although some criteria relating to trial heterogeneity are mentioned in the ITC Report, such as demographic characteristics (ITC Report section 3.1.2), blinding (ITC Report Table 6) and other aspects of RCT quality (ITC Report Appendix 10), these are not discussed systematically in relation to whether the RCTs were adequately comparable and of sufficient

quality to be included in meta-analyses. Exceptions (explained further below) are that limited sensitivity analyses were conducted to explore the impact of blinded versus open-label RCTs for some outcomes; and, for the exacerbations outcome, RCTs were classified according to how they defined exacerbations and this influenced their eligibility for analysis.

The CS and ITC report do not mention the outcome assessment times for the individual omalizumab trials and the company's specification of 16 ± 4 weeks and 52 ± 4 weeks is unnecessarily imprecise for some analyses. To improve precision, the ERG has added more accurate outcome assessment timing information in our summary of the ITC results (section 3.4).

The 'feasibility assessment' (ITC Report Appendix 4) lists 22 outcomes, of which seven were selected without explanation for inclusion in ITC analyses. These seven outcomes are the same as were included in the direct comparison meta-analysis (
Table 9).

~~*As would be expected, the reslizumab versus placebo RCTs which were included in the direct comparison meta-analysis were also included in the ITC, with one exception: for the AQLQ outcome assessed at 16 ± 4 weeks, the ITC included four reslizumab versus placebo RCTs whereas the direct comparison meta-analysis had included three (*~~
~~*Table* 9*). The difference is accounted for by the RCT by Castro and colleagues (Res-5-0010)[22] being included in the ITC but not the direct comparison meta-analysis for this outcome, but the CS does not explain this discrepancy.*~~

The CS does not provide a rationale for excluding any specific outcomes from the ITC, apart from %predicted FEV1. The ITC Report (section 3.4.1) states that the change from baseline in FEV1 was selected as an endpoint in preference to the change in %predicted FEV1 since, according to the feasibility assessment at 16 ± 4 weeks, FEV1 was reported in more studies (n=8) than %predicted FEV1 (n=6). According to a clinical expert advising the ERG, this is reasonable, since FEV1 and %predicted FEV1 would likely show similar effects. However, another expert commented that the % FEV1 is less influenced by variation in trial participant characteristics such as age and sex.

Statistical methods for the ITC

The statistical analysis approach is summarised in the ITC Report (section 2.2). Methods for the extraction of data from the RCTs and the imputation of missing values were the same as

those reported for the direct comparison meta-analysis (see section 3.1.7.1). The analysis models were also the same as those employed for the direct comparison meta-analysis: a Bayesian framework was employed for analysing time-standardised counts of clinically significant exacerbations, whilst a standard frequentist approach based on the inverse variance weighted method was employed for analysing all other outcomes. In the frequentist analysis the fixed-effect estimate was accepted unless statistical heterogeneity was significant (based on Cochran's Q and/or the I^2 statistic), otherwise the random-effects estimate was used. In the Bayesian analysis the DIC was used to decide whether the fixed-effects or random-effects model had the best fit, based on the same criteria as applied in direct comparison meta-analysis (section 3.1.7.1). The ERG cautions against selecting fixed or random effects models based solely on the DIC since model plausibility is arguably more important than model fit.[26]

The ITC Report states that direct pairwise comparisons were first conducted in order to assess the heterogeneity between studies and to generate results to be used for the indirect comparisons. The ITC reports results of direct comparisons both for the reslizumab versus placebo trials (i.e. duplicating the direct comparison meta-analysis results already given in the CS) and for the omalizumab versus placebo trials. We have summarised the direct comparison results for omalizumab versus placebo in the ITC results section of this report (section 3.4).

Frequentist indirect comparisons were based on the method of Bucher and colleagues[29] which is a standard approach for combining normally-distributed effect estimates. Continuous outcomes were assumed to be normally distributed and were not transformed. For odds ratios obtained from binary outcomes, a natural logarithm transformation was applied. For each indirect comparison the 95% CI was calculated and a standard two-sided t-test was performed; p-values <0.05 were interpreted to mean that reslizumab performed better than omalizumab.

The Bayesian analysis of exacerbation rates was performed with WinBUGS using the Markov Chain Monte Carlo simulation method. Three chains were simulated and their convergence was assessed using an accepted method (examination of history and Gelman-Rubin plots). The same numbers of iterations were used for both burn-in and monitoring of parameters: 20,000 for the fixed-effects model, and 100,000 for the random-effects model (ITC Report section 2.2.5.3). Although limited information about the methods is provided, the approach is consistent with NICE DSU guidance for meta-analysis and the ERG agrees that the methods were generally appropriate.

As stated in the ITC Report (section 3.4.1), a limited number of sensitivity analyses were conducted, for some ITC outcomes (see below), to explore the impact of including or excluding open-label trials from the analysis. The ERG acknowledges that opportunities for sensitivity analyses were generally limited by the small numbers of trials available for each outcome analysed.

ITC network

The ITC Report states that the indirect comparison of omalizumab versus reslizumab via BSC is the difference between the effect of omalizumab versus BSC and the effect of reslizumab versus BSC (ITC Report section 2.2.4.1). It also states that the BSC arms were considered to have a similar effect as placebo arms; in other words, arms including BSC + placebo were considered as equivalent to BSC arms (ITC Report section 2.3). However, no justification is provided for this, and the CS mentions a potential placebo effect observed in trials 3082 and 3083 (CS section 5.3.2.1) which suggests that placebo and BSC might not be equivalent. Clinical expert advice to the ERG is that placebo effects are well-known and common in asthma trials.

As shown in Figure 2, the ITC network for comparing reslizumab against omalizumab is very simple and contains only direct pairwise comparisons. As such, the consistency assumption of network meta-analysis is not applicable. The number of trials available for each arm in the network varied with the outcome being analysed. Although five reslizumab and 16 omalizumab RCTs were identified in the company's systematic review of clinical effectiveness, after applying various (poorly explained) exclusion criteria, the numbers of RCTs which were included in the network ranged from 1 to 5 for reslizumab and 1 to 4 for omalizumab (
Table 9).

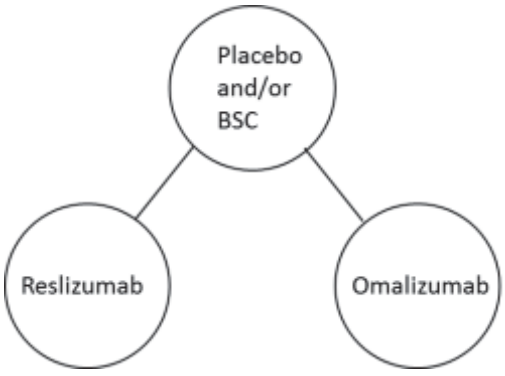


Figure 2 ITC network diagram

Similarity and homogeneity assumptions

Two key assumptions need to be justified in order for an ITC to be considered robust. All trials included in the network should be adequately homogeneous, meaning that the participant characteristics, interventions, comparators, and study designs should be comparable enough to enable pooling of trial results. And the trials should also satisfy the assumption of similarity, meaning that they are similar for modifiers of relative treatment effect.[30] Aspects of study quality (e.g. risk of bias) also influence whether the results of an ITC may be robust.

Homogeneity was not adequately assessed, since the company only compared participant characteristics broadly across all the trials identified for potential inclusion, rather than among those actually included for each outcome (ITC Report section 3.1.2.2). Based on the information provided in the ITC Report (Appendix 7), the participants' characteristics appear to be broadly homogeneous across the reslizumab and omalizumab trials, but the baseline characteristics provided for the omalizumab trials are less detailed than those given for reslizumab so comparisons are difficult to make. As noted above (section 3.1.3.2), there were some differences in baseline characteristics between the reslizumab trials. A notable difference is that out of the 21 reslizumab and omalizumab trials potentially eligible for the ITC, only four reslizumab trials (3082, 3083, 3081, Res-5-0010) specified blood eosinophil levels as an inclusion criterion.

In trial 3084 the total randomised population included some patients with blood eosinophil concentrations <400 cells/μL. The ITC Report does not state whether data from all patients in trial 3084 or from a subgroup with a blood eosinophil count of ≥400 cells/μL were used in the ITC. We have assumed that the whole population for trial 3084 was analysed in the ITC, as this would be consistent with the reported direct comparison meta-analysis approach. Given that the population most relevant to the scope ('elevated blood eosinophils') is patients with blood eosinophils ≥400 per μL, a case could be made for analysing this subgroup instead of, or in addition to, the whole population in trial 3084 (e.g. in a sensitivity analysis), although this was not done by the company.

The assumption of similarity is not mentioned in the ITC Report. The summaries of trial characteristics provided (ITC Report Appendix 9 and CS Table 18) show that participants were generally similar at baseline across the reslizumab and omalizumab trials included in the indirect comparison, apart from in the number of exacerbations they had experienced in the previous year. Participants in the omalizumab trials had on average more asthma exacerbations in the previous year than those in the reslizumab trials: the range of means was, respectively, 1.9 to 5.48 exacerbations per year (reported in 4 RCTs) and 1.9 to 2.1 exacerbations per year (reported in 3 RCTs). This difference suggests that populations in the omalizumab RCTs may have had more severe asthma at baseline than those in the reslizumab RCTs.

The company conducted a quality assessment of the RCTs (ITC Report Appendix 10) but this did not inform trial eligibility decisions for the ITC. However, sensitivity analyses were conducted to explore the impact of excluding open-label omalizumab RCTs where sufficient trials were available. It is not stated in the ITC Report whether sensitivity analyses were planned a priori or were post-hoc. Ideally, a priori analyses should have been performed to reduce the possibility of bias that could result from over-fitting meta-analyses to the study results once they are known.

Summary of the ERG's critique of the ITC

Overall, the analysis approach employed for the ITC was appropriate and is clearly reported. However, there are several limitations to the evidence that was included in the ITC:

- The process for determining eligibility of RCTs for analysis is unclear, so it is unclear whether any additional outcomes relevant to the NICE scope were omitted from the ITC
- An assumption is made that placebo arms of trials are equivalent to BSC arms, but no justification is provided; a potential placebo effect was identified which suggests this assumption may not be appropriate;
- No discussion is provided as to whether different BSC arms in the trials are equivalent to BSC in current NHS practice (e.g. where the comparator assumed to be BSC was described as "optimised asthma therapy" in the EXALT trial or a "control group" in the QUALITX trial);
- The definitions of clinically significant exacerbations appear to have been applied inconsistently, meaning that some omalizumab trials may have been inappropriately excluded from the ITC;

- Based on the history of exacerbations, participants in the omalizumab trials appear to have had more severe asthma at baseline than those in the reslizumab trials;

These limitations suggest that results of the ITC may not be reliable. The company acknowledges that the ITC had limitations and, given that the ITC did not yield statistically significant results, the ITC Report states that the results should be interpreted with caution (ITC Report section 4).

Validity of the indirect comparison results

The CS and ITC Report do not discuss whether similar indirect comparisons have been published and did not compare their findings to any related existing indirect comparisons (e.g. as employed in the NICE STA of mepolizumab). However, we are unaware of any other ITC or other types of network meta-analysis that have included both reslizumab and omalizumab.

3.1.7.3 Role of the clinical effectiveness synthesis in informing the company's economic analysis

The results from the company's direct comparison of reslizumab against placebo and the ITC of reslizumab against omalizumab do not directly inform the company's economic analysis. The CS states in the economic analysis section (CS section 5.3.2.3) that "the impact of omalizumab on the number of exacerbations was estimated based on the relative rate of exacerbations obtained from an NMA at 52 weeks versus BSC (estimate of 0.82)".This statement refers to the ITC report.[16] However, the ITC Report does not present any direct comparison results for omalizumab versus BSC and does not provide a rate ratio of exacerbations of 0.82 from any analysis.

3.2 Overall summary statement of the company's approach

Overall, the company's approach to the clinical effectiveness assessment was reasonable, being based on standard systematic review methods which are generally well reported. A summary of our critique of the company's approach is given in Table 10, according to the standard CDR criteria.

Table 10 Quality assessment (CRD criteria) of CS review

CRD Quality Item: score Yes/ No/ Uncertain with comments	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address	Yes. Note that searches were restricted to RCTs. The CS does not discuss whether any relevant non-

the review question?	randomised studies might have been missed.
2. Is there evidence of a substantial effort to search for all relevant research? i.e. all studies identified	Yes. The ERG did not find any additional studies apart from a trial of omalizumab which had been published after the date of the company's searches.
3. Is the validity of included studies adequately assessed?	Partly. Yes for trials 3082, 3083, 3081 and 3084. No for Res-5-0010, although a separate quality assessment for this trial was provided to the ERG on request.
4. Is sufficient detail of the individual studies presented?	Partly. Yes for trials 3082, 3083, 3081 and 3084. No for Res-5-0010, and the ERG has had to obtain information on this trial from the trial publication.
5. Are the primary studies summarised appropriately?	Partly. Yes for trials 3082, 3083, 3081 and 3084. Only the results of Res-5-0010 are summarised in the CS, not methods. Note that whilst the summary of primary trials is appropriate, reasons for missing outcomes in the company's direct meta-analysis of reslizumab versus placebo are not explained.

3.3 Direct treatment comparison results: reslizumab versus placebo

The CS presents extensive results from the trials which compared reslizumab against placebo. Below we have summarised the results from these trials and also the results of the company's direct comparison meta-analyses where available, for outcomes which are relevant to the NICE scope. Additional supporting information for outcomes not specified in the NICE scope is provided in section 3.3.6 for completeness.

3.3.1 Asthma control (ACQ scores)

Five RCTs reported changes in ACQ scores over 16 weeks (Table 11). The sample sizes stated in the CS for this outcome are smaller than both the number randomised and (where defined) the FAS for all the trials except Res-5-0010 (for analysis population definitions see Table 7). Reasons for the missing data are not explained in the CS. For trials 3082 and 3083 the discrepancy is small (<2% of the number randomised) but in trials 3081 and 3084 the proportion of missing data compared to the number randomised is considerable, ranging from 13.8% (55/398) in the reslizumab arm of trial 3084 to 20% (21/105) in the placebo arm of trial 3081.

Improved asthma control is indicated by a decrease in ACQ scores, and the scores consistently decreased to a greater extent in the reslizumab group then the placebo group. The differences statistically favour reslizumab over placebo for asthma control, although the results for trial Res-5-0010 border on statistical non-significance, with the confidence intervals only narrowly excluding zero. Note that the results for trial 3084 (which are of

borderline statistical significance) are for the total population, which included some patients with baseline blood eosinophil levels <400 per µL. When a subgroup of patients with blood eosinophil levels ≥400 per µL was analysed in this trial (reslizumab n=77, placebo n=19), the mean difference was not statistically significant: –0.49 (95% CI –1.01, 0.03); p=0.0643 (CS Table 55).

Table 11 ACQ score: mean change from baseline at 16±1 weeks

Trial	Reslizumab	Placebo	Mean difference (95% CI)	Source
3082[a]	–0.94[b] (n=242)	–0.68[b] (n=241)	–0.27 (–0.40, –0.13); p=0.0001	CS Table 25
3083[a]	–0.86[b] (n=230)	–0.66[b] (n=228)	–0.20 (–0.33, –0.07); p=0.0032	CS Table 35
3081[c]	–0.94[b] (n=91)	–0.58[b] (n=84)	–0.35 (–0.63, 0.08); p=0.0129	CS Table 47
3084[c d]	–0.91 (n=343)	–0.70 (n=83)	–0.20 (–0.39, –0.004); p=0.0457	CS Table 55
Res-5-0010[e]	–0.7 (n=53)	–0.3 (n=53)	–0.38 (–0.76, 0.01); p=0.054	Castro et al.[22]

[a] change calculated as weighted average across 16 weeks
[b] least squares mean
[c] change calculated at week 16
[d] data are for total population with baseline eosinophils <400 per µL and ≥400 per µL
[e] change calculated at week 15

The CS reports results of direct comparison meta-analysis of the ACQ scores at 16±1 weeks, but the input data reported in the CS for meta-analysis (CS Table 61) differ in some respects from those given in the CS tables reporting the individual trial results. For trials 3082 and 3083, the CS presents mean differences only for the analysis based on a weighted average across 16 weeks (Table 11) whereas the meta-analysis used values from an analysis at week 16 (CS Table 61). For trial 3081, the input data for the meta-analysis (CS Table 61) do not concur with ACQ results reported elsewhere in the CS for this trial (CS Table 47). However, we believe that the magnitude and direction of these inconsistencies would be unlikely to introduce bias in favour of reslizumab for this outcome.

Results of the direct comparison meta-analysis of ACQ scores are given in Table 12 and the forest plot is shown in Figure 3. A statistically significantly greater decrease in the ACQ mean score in the reslizumab group indicates that this group achieved a larger improvement in asthma control than the placebo group. There was no difference between the random- and fixed- effect models, and heterogeneity between the studies was low (I^2=24%).

Meta-analysis of ACQ scores at 52 weeks was not feasible due to lack of data.

Table 12 Direct comparison meta-analysis: ACQ score change over 16±1 weeks

	Difference between means, reslizumab versus placebo (95% CI)	Source
Fixed-effects model	–0.24 (–0.32; –0.17)	CS Table 62
Random-effects model	–0.24 (–0.32; –0.17)	
P-value of the Cochran test	0.2639	
I^2	24%	

Abbreviations: ACQ, Asthma Control Questionnaire; CI, confidence interval.
A negative change from baseline indicates that reslizumab is better than placebo

FE, fixed effects; RE, random effects

Figure 3 Forest plot for the change from baseline in ACQ at 16±1 weeks

The CS does not discuss these changes in ACQ scores in relation to the ACQ score cut-points for uncontrolled asthma (score ≥1.5) and well controlled asthma (score ≤0.75).

ACQ responder analysis results are presented in the CS for trial 3082 (week 52; CS section 4.7.1.5), trial 3083 (weeks 16 and 52; CS section 4.7.2.5) and trial 3081 (week 4; CS section 4.7.3.7). In each case the proportion of responders was [redacted] in the reslizumab-treated than the placebo group. However, the analysis is limited as it was not controlled for multiple testing and we are unclear whether it was planned or post-hoc. The CS presents graphs showing the proportions of responders at 4-weekly intervals (CS

Figures 11, 21, 30) and each time point appears to have been tested statistically, which would give a large number of multiple comparisons. We note that the responder proportion in the placebo group was [redacted] (e.g. [redacted] in trial 3082 at 52 weeks) whilst by comparison the difference in responder rates between reslizumab and placebo groups was [redacted] (e.g. [redacted] responders in the reslizumab than the placebo group in trial 3082 at 52 weeks). Due to the limitations in the analysis [redacted] the ACQ responder analysis results should be treated with caution.

3.3.2 Exacerbations

Two of the company's trials, 3082 and 3083, provided information on exacerbations, and in both trials the primary outcome was the frequency of clinically significant asthma exacerbations (referred to in the trials as 'clinical asthma exacerbations') over 52 weeks. The CS presents extensive results for exacerbations from these trials, including a range of sensitivity analyses. Below we have summarised the information which appears most pertinent to the company's economic analysis. Unless stated otherwise, the sensitivity analyses did not alter the findings reported below.

An additional trial, Res-5-0010,[22] which had a duration of 15 weeks, also provides some information on exacerbation rates, but this is only mentioned briefly in the CS. The Res-5-0010 trial reported that four patients in the reslizumab group (8%) and 10 in the placebo group (19%) had an exacerbation (odds ratio 0.33 (95% CI 0.10, 1.15); p=0.0833).[22]

As summarised below, the CS presents the results of the two pivotal trials 3082 and 3083 as the overall frequencies of exacerbations (Table 13), and as the frequencies of exacerbations which required systemic corticosteroids for ≥3 days (Table 14), required oral corticosteroids for ≥3 days (Table 15), or required a hospitalisation and/or emergency room visit (Table 16). For overall exacerbations and those requiring corticosteroids, the frequencies were lower in the reslizumab group than in the placebo group and the differences were statistically significant with rate ratios in favour of reslizumab. However, for the subgroup of exacerbations requiring a hospitalisation and/or emergency room visit (Table 16) the rate was not statistically significant.

Table 13 Rate of clinical asthma exacerbations over 52 weeks

Trial	Adjusted mean frequency		Rate ratio (95% CI)	Source
	Reslizumab	Placebo		
3082	0.90 (n=245)	1.80 (n=244)	0.50 (0.37, 0.67); p<0.0001	CS Table 20

3083	0.86 (n=232)	2.11 (n=232)	0.41 (0.28, 0.59); p<0.0001	CS Table 30

Table 14 Exacerbations requiring systemic corticosteroids for ≥3 days over 52 weeks

Trial	Adjusted mean frequency		Rate ratio (95% CI)	Source
	Reslizumab	Placebo		
3082	0.72 (n=245)	1.60 (n=244)	0.45 (0.33, 0.62); p<0.0001	CS Table 22
3083	[redacted]	[redacted]	[redacted]	CS Table 32

Table 15 Exacerbations requiring oral corticosteroids for ≥3 days over 52 weeks

Trial	Adjusted mean frequency		Rate ratio (95% CI)	Source
	Reslizumab	Placebo		
3082	0.70 (n=245)	1.59 (n=244)	0.44 (0.32, 0.61); p<0.0001	CS Table 22
3083	[redacted]	[redacted]	[redacted]	CS Table 32

Table 16 Exacerbations requiring hospitalisation and/or emergency room visit over 52 weeks

Trial	Adjusted mean frequency		Rate ratio (95% CI)	Source
	Reslizumab	Placebo		
3082	0.14 (n=245)	0.21 (n=244)	0.66 (0.32, 1.36); p=0.2572	CS Table 22
3083	[redacted]	[redacted]	[redacted]	CS Table 32

The results from each of the pivotal trials presented in the CS also include an analysis of the probability of patients not experiencing a clinically significant asthma exacerbation by week 52, based on a Kaplan-Meier analysis (Table 17). Kaplan-Meier curves are provided by the company (CS Figures 12 & 22). In both trials patients in the reslizumab group were less likely to experience a clinically significant exacerbation, with the hazard ratios being statistically significant, favouring reslizumab over placebo (Table 17).

Table 17 Kaplan-Meier probability of not experiencing a clinical asthma exacerbation by week 52

Trial	Reslizumab	Placebo	Hazard ratio (95% CI)	Source
3082	61.3% (95% CI 54.7%, 67.2%) (n=245)	44.2% (95% CI 37.7%, 50.5%) (n=244)	0.58 (0.44, 0.75); p<0.0001	CS Table 26

3083	73.2% (95% CI 66.8%, 78.6%) (n=232)	51.9% (95% CI 45.0%, 58.3%) (n=232)	0.49 (0.35, 0.67); p<0.0001	CS Table 36

As specified in the CS, analysis of differences between the reslizumab and placebo groups in the median time to the first clinically significant exacerbation was specified as a secondary outcome in both of the pivotal trials. However, the CS points out that the median time to a first clinically significant exacerbation could not be calculated for the reslizumab group in either trial, as fewer than 50% of patients in the reslizumab groups experienced clinically significant exacerbations.

Direct comparison meta-analysis of exacerbations

The company conducted two meta-analyses of exacerbation rates. These were for the overall rate of clinically significant exacerbations, and for the numbers of patients hospitalised due to clinically significant exacerbations (CS section 4.9.2.6).

Input data for the meta-analysis of overall exacerbation rate are given in Table 18 and the results of the meta-analysis are given in Table 19. As explained in the methods (ERG report section 3.1.7), this analysis employed a Bayesian framework which modelled the number of person-years at risk of clinically significant exacerbations (an approach recommended by NICE[27]). The sample sizes stated in the CS for this outcome (Table 18) are smaller than both the number randomised and the FAS for trials 3082 and 3083 (for analysis population definitions see Table 7). Reasons for these missing data are not explained in the CS; however, the discrepancy is small (0.8% to 2.1% of the number randomised).

Table 18 Clinically significant exacerbations

Study, Follow up	Reslizumab versus placebo				
	Treatment arm	**N**	**Exacerbation rate**	**Number of exacerbations**	**Person-years**
Res-05-0010, over 15 weeks	Reslizumab	53	NR	4	15.29
	Placebo	53	NR	10	15.29
3082, over 52 weeks	Reslizumab	243	0.90	47	243.00
	Placebo	241	1.80	94	241.00
3083, over 52 weeks	Reslizumab	230	0.86	45	230.00
	Placebo	227	2.11	110	227.00

NR: not reported. Source: CS Table 67

The fixed-effects model but not the random-effects model indicate that clinically significant exacerbations were statistically significantly less likely in the reslizumab group, with a Bayesian probability of 100% from the fixed-effects analysis that reslizumab always performs better than placebo (Table 19). The CS states that despite the small number of trials included in the analysis and the credibility interval associated with the random-effects model including 1, reslizumab was still associated with a probability of performing better than placebo of 97%.

Table 19 Direct comparison meta-analysis: clinically significant exacerbations

	Median hazard ratio (95% CI)	Probability	DIC	Source
Fixed-effects model	0.44 (0.35 to 0.56)	100%	78.06	CS Table 68
Random-effects model	0.43 (0.17 to 1.10)	97%	78.81	

CI, confidence interval; DIC, deviance information criterion.
A hazard ratio <1 means that reslizumab is better than its comparator.
Probability is the Bayesian probability that a treatment performs better than its comparator. If Probability=100%, reslizumab always performs better than placebo.

Direct comparison of the patients hospitalised due to exacerbations was conducted for a 15 week period based on results from the trial Res-5-0010 and for a 52 week period based on the results from the two pivotal company trials 3082 and 3083.

The RES-5-0010 trial had 53 patients in each group. Results over 15 weeks identified only one hospitalisation event in the reslizumab group (1.9%) and zero in the placebo group (0%) (CS Table 69).

Input data for the direct comparison meta-analysis of patients hospitalised due to exacerbations over 52 weeks are given in Table 20 and the results of the meta-analysis are given in Table 21. The sample sizes stated in the CS for this outcome (Table 20) are smaller than both the randomised population and FAS for trials 3082 and 3083 (for analysis population definitions see Table 7). Reasons for these missing data are not explained in the CS; however, the discrepancy is small (0.8% to 2.1% of the number randomised).

Table 20 Patients hospitalised due to exacerbations up to 52 weeks

Trial	Reslizumab versus placebo	Source

	Treatment arm	N	Number of patients hospitalised	CS Table 70
3082	Reslizumab	243	9	
	Placebo	241	11	
3083	Reslizumab	230	5	
	Placebo	227	8	

As mentioned in the CS, few patients were hospitalised over the course of the trials (Table 20). While the number of patients hospitalised was lower in the reslizumab arms of the RCTs, results from the direct comparison of reslizumab versus placebo were not statistically significant. No heterogeneity was detected by the I^2 test (Table 21).

Table 21 Direct comparison meta-analysis: patients hospitalised due to exacerbations up to 52 weeks

	Odds ratio, reslizumab versus placebo (95% CI)	Source
Fixed-effects model	0.73 (0.36; 1.47)	CS Table 71
Random-effects model	0.73 (0.36; 1.47)	
P-value of the Cochran test	0.72	
I^2	0%	

The CS states that results for this outcome are mean differences; however, they are odds ratios

3.3.3 Lung function (FEV1 and other outcomes)

FEV1

Five trials reported changes in FEV1 over 16 weeks (Table 22). For all these trials the sample sizes stated in the CS for this outcome are smaller than both the number randomised and, where trials defined it, the FAS (for analysis population definitions see Table 7). Reasons for the missing data are not explained in the CS. The missing data as a proportion of the number randomised ranges from 1.9% (1/53) in both arms of trial Res-5-0010 to 20% (21/105) in the placebo arm of trial 3081. Across both arms of the pivotal trials 3082 and 3083 the proportion of missing data relative to the number randomised ranges from 5.3% to 7.8%.

In all the trials improvements in FEV1 significantly favoured reslizumab over placebo, except for trial 3084 where the mean difference was not statistically significant. However, this trial included some patients with baseline blood eosinophil levels <400 per µL. When a subgroup of patients with blood eosinophil levels ≥400 per µL was analysed in this trial (reslizumab

n=77, placebo n=19), the mean difference statistically favoured reslizumab: 0.27 (95% CI 0.01, 0.53); p=0.0436 (CS Table 54).

Table 22 FEV1: mean change from baseline (L) at 16±1 weeks

Trial	Reslizumab	Placebo	Mean difference (95% CI)	Source
3082	0.20 (n=232)	0.13 (n=228)	0.07 (0.001, 0.14); p=0.0483	CS Table 23
3083	0.25 (n=214)	0.15 (n=214)	0.10 (0.02, 0.18); p=0.0109	CS Table 33
3081	0.24 (n=91)	0.05 (n=84)	0.17 (0.04, 0.29); p=0.0118	CS Table 40
3084[a]	0.25 (n=344)	0.18 (n=83)	0.07 (–0.03, 0.17); p=0.1719	CS Table 54
Res-5-0010	0.18 (n=52)	–0.08 (n=52)	0.24 (0.09, 0.39); p=0.0023	Castro et al.[22]

Changes were calculated at 16 weeks except for Res-5-0010 (15 weeks)
[a] data are for total population with baseline eosinophils <400 per µL and ≥400 per µL

Two trials reported changes in FEV1 over 52 weeks (Table 23). As with the analysis at 16±1 weeks, the sample sizes reported in the CS for this outcome were smaller than both the number randomised and the FAS for trials 3082 and 3083. The missing data as a proportion of the number randomised ranges from 0.8% to 2.1%.

Table 23 FEV1: mean change from baseline (L) at 52 weeks

Trial	Reslizumab	Placebo	Mean difference (95% CI)	Source
3082	0.24 (n=243)	0.08 (n=241)	Not reported	CS Table 59
3083	0.23 (n=230)	0.12 (n=227)	Not reported	CS Table 59

The CS reports results of direct comparison meta-analysis of the FEV1 outcome at 16±1 weeks and 52 weeks, based on the input data shown in Table 22 and Table 23. The forest plot for this analysis (from CS Figure 37) is shown in Figure 4. The pooled effects estimates were almost identical for the fixed and random effects models (Table 24). Reslizumab was statistically favoured over placebo at both 16±1 weeks and 52 (the 95% CI excludes zero), although with moderate statistical heterogeneity at 16±1 weeks (indicated by I^2=41%).

Table 24 Direct comparison meta-analysis: FEV1 change over 16 and 52 weeks

	Difference between means, reslizumab versus placebo (95% CI)		Source
	16±1 weeks	**52 weeks**	CS Tables 58 & ~~59~~ 60
Fixed-effects model	0.12 (0.08; 0.16)	0.13 (0.08; 0.18)	
Random-effects model	0.13 (0.07; 0.18)	0.13 (0.08; 0.18)	
P-value of the Cochran test	0.15	0.67	
I^2	41%	0%	

CI, confidence interval; FEV1, forced expiratory volume in one second.

FE, fixed effects; RE, random effects

Figure 4 Forest plot for the change from baseline in FEV_1 at 16±1 weeks

Other lung function outcomes

The company did not meta-analyse any other lung function outcomes. However, the CS presents trial results for changes in the % predicted FEV1 (indicative of age-normal forced expiratory flow in one second), FVC (forced vital capacity), and $FEF_{25-75\%}$ (average expiratory flow rate at the middle part of forced expiration). We have summarised these outcomes briefly below as they provide additional clinical information (the NICE scope does not specify a focus on, or exclusion, of specific lung function outcomes). For all three of these outcomes the sample sizes reported in the CS are smaller than the number randomised, but the CS does not explain the missing data.

Information on the % predicted FEV1 change from baseline was available at 16±1 weeks from five trials (Table 25) and at 52 weeks from two trials (Table 26), although the mean difference at 16±1 weeks was not reported for two of the trials, and there were some differences between the trials in the way the results were calculated. The improvement in % predicted FEV1 consistently favoured reslizumab over placebo, both at the 16±1 week and 52 week assessments. However, according to clinical experts these changes are small and not clinically meaningful.

Table 25 % predicted FEV1: mean change from baseline at 16±1 weeks

Trial	Reslizumab	Placebo	Mean difference (95% CI)	Source
3082[a]	Not reported	Not reported	4.2 (2.08, 6.25); p<0.0001	CS page 90
3083[a]	Not reported	Not reported	3.05 (1.01, 5.10); p=0.0035	CS page 105
3081[b]	7.5 (n=91)	0.8 (n=84)	Not reported	CS Table 46
3084[b c]	7.8 (n=344)	5.5 (n=83)	Not reported	CS Table 55
Res-5-0010[d]	6.19 (n=52)	−2.44 (n=52)	7.98[e] (3.30, 12.65); p=0.0010	Castro et al.[22]

[a] change calculated as weighted average across 16 weeks
[b] change calculated at week 16
[c] data are for total population with baseline eosinophils <400 per µL and ≥400 per µL
[d] change calculated at week 15
[e] least squares mean

Table 26 % predicted FEV1: mean change from baseline at 52 weeks

Trial	Reslizumab	Placebo	Mean difference (95% CI)	Source
3082[a]	Not reported	Not reported	3.9 (1.82, 5.96); p=0.0002	CS page 90
3083[a]	Not reported	Not reported	3.18 (1.12, 5.23); p=0.0025	CS page 105

[a] change calculated as weighted average across 52 weeks

Information on the FVC change from baseline was available at 16±1 weeks from five trials (Table 27) and at 52 weeks from two trials (Table 28), although there were some differences between the trials in the way the results were calculated. Results at both 16±1 weeks and 52 weeks consistently statistically favoured reslizumab over placebo, apart from trial 3084 where the results reported are for a combined total trial population of patients with blood eosinophil concentrations ≥400 per µL and blood eosinophil concentrations <400 per µL. In this population the difference in change from baseline in FVC between reslizumab and placebo was not significantly different from zero.

Table 27 FVC: mean change from baseline (L) at 16±1 weeks

Trial	Reslizumab	Placebo	Mean difference (95% CI)	Source
3082[a]	Not reported	Not reported	0.13 (0.05, 0.22); p=0.0011	CS page 89
3083[a]	Not reported	Not reported	0.08 (0.01, 0.15); p=0.0326	CS page 105
3081[a]	0.30[d] (n=102)	0.17[d] (n=103)	0.13 (0.02, 0.24); p=0.0174	CS Table 44
3084[b]	0.24 (n=344)	0.22 (n=83)	0.01 (−0.10, 0.12): p=0.8361	CS Table 55
Res-5-0010[c]	0.18 (n=52)	−0.13 (n=52)	0.27[d] (0.08, 0.46); p=0.0054	Castro et al.[22]

[a] change calculated as weighted average across 16 weeks
[b] change calculated at week 16; data are for total population with baseline eosinophils <400 per µL and ≥400 per µL
[c] change calculated at week 15
[d] least squares mean

Table 28 FVC: mean change from baseline (L) at 52 weeks

Trial	Reslizumab	Placebo	Mean difference (95% CI)	Source
3082[a]	Not reported	Not reported	0.12 (0.04, 0.20); p=0.0040	CS page 89
3083[a]	Not reported	Not reported	0.08 (0.01, 0.16); p=0.0202	CS page 105

[a] change calculated as weighted average across 52 weeks

Information on the $FEF_{25-75\%}$ change from baseline was available at 16±1 weeks from two trials (Table 29), in both cases based on the full analysis set, although there were some differences between the trials in the way the results were calculated. Unlike the other lung function outcomes at 16±1 weeks, the differences in the mean change of $FEF_{25-75\%}$ from baseline between reslizumab and placebo were not significantly different from zero. Note that in trial 3084 some patients had blood eosinophil concentrations <400 per µL.

Table 29 $FEF_{25-75\%}$: mean change from baseline (L/s) at 16 weeks

Trial	Reslizumab	Placebo	Mean difference (95% CI)	Source
3081[a]	[redacted]	[redacted]	[redacted]	CS Table 45
3084[c]	0.23 (n=341)	0.20 (n=81)	0.06 (–0.13, 0.26); p= 0.5109	CS Table 55

[a] change calculated as weighted average across 16 weeks
[b] least squares mean
[c] change calculated at week 16; data are for total population with baseline eosinophils <400 per µL and ≥400 per µL

3.3.4 Adverse events

Details of adverse events presented in the CS are based on the open-label study 3085, which enrolled patients from trials 3081, 3082 and 3083. Patients had a 104-week treatment period and a 90-day follow-up period, with a mean exposure of 356.4 days to the study drug for reslizumab-experienced patients and 335.4 days for the reslizumab-naïve patients (previously placebo treated).

The broad classes of adverse events which affected at least 5% of patients in the clinical trials and the extension study 3085 are shown in Table 30. *Overall, the incidence of any adverse event was more frequent in the placebo arm. While mild adverse events were more frequent in the reslizumab arm (3/3 trials reporting these), moderate adverse events were more frequent in the placebo arm (3/3 trials reporting these). Serious adverse events were more frequent in the placebo arm in 2 of 4 trials which reported these.* ~~*events in all categories (mild, moderate, severe) occurred in both the reslizumab and placebo groups,*~~

~~*with a tendency for most categories to be slightly more frequent in the reslizumab group.*~~
Events classed as treatment-related were broadly similar in frequency in the reslizumab and placebo groups. Only one death occurred during the randomised trials, in the placebo group of trial 3082.

The types of adverse event that affected at least 5% of patients in either treatment group are shown for the clinical trials and the extension study 3085 in Table 31. Blank cells in the table indicate where data were not reported in the CS, and the pattern of data availability might be suggestive of selective reporting of certain adverse events, e.g. sinusitis and upper respiratory tract infection were relatively frequent in trial 3082 but not reported for trial 3083. Overall, where reported, the individual types of adverse events occurred in similar frequencies in the reslizumab and placebo groups and the only cases where a particular type of adverse event was markedly more frequent in the reslizumab group than the placebo group were for upper respiratory infection in trial 3082 (16% versus 13%) and headache, both in trial 3083 (14% versus 7%) and trial 3081 (11% versus 6%).

Table 30 Adverse events affecting ≥5% of patients in reslizumab trials (safety analysis set)

Adverse events (AE), n (%)	Trial 3082 (CS Table 80)		Trial 3083 (CS Table 82)		Trial 3081 (CS Table 84)		Trial 3085 (CS Table 91)	
	Reslizumab N=245	Placebo N=243	Reslizumab N=232	Placebo N=232	Reslizumab N=103	Placebo N=105	Reslizumab N=571	Placebo N=480
Any AE[a]	197 (80)	206 (85)	177 (76)	201 (87)	61 (59)	66 (63)	385 (67)	359 (75)
Mild	68 (28)	41 (17)	67 (29)	36 (16)	NR	NR	142 (25)	115 (24)
Moderate	107 (44)	133 (55)	98 (42)	140 (60)	NR	NR	196 (34)	213 (44)
Severe	22 (9)	32 (13)	12 (5)	25 (11)	7 (7)	4 (4)	47 (8)	31 (6)
Treatment-related AE[b]	36 (15)	36 (15)	34 (15)	27 (12)	12 (12)	8 (8)	41 (7)	49 (10)
Mild	24 (10)	23 (9)	22 (9)	14 (6)	NR	NR	19 (3)	27 (6)
Moderate	9 (4)	13 (5)	11 (5)	13 (6)	NR	NR	19 (3)	18 (4)
Severe	3 (1)	0	1 (<1)	0	1	1 (<1)	3 (<1)	4 (<1)
Serious AE	24 (10)	34 (14)	18 (8)	23 (10)	4 (4)	1 (<1)	45 (8)	33 (7)
Deaths	0	1 (<1)	0	0	0	0	2 (<1)	1 (<1)
AE leading to discontinuation	4 (2)	8 (3)	8 (3)	9 (4)	6 (6)	10 (10)	12 (2)	6 (1)
AE up to follow-up period							367 (64)	344 (72)
AE in the follow-up period							82 (14)	78 (16)

NR: not reported
[a] Treatment-emergent AEs, which included all non-serious and serious AEs that began or worsened after treatment with study drug.
[b] As assessed by the investigator.

Table 31 Adverse events occurring in ≥5% of patients in either treatment group (safety analysis set)

Adverse events (AE), n (%)	3082 (CS Table 81)		3083 (CS Table 83)		3081 (CS Table 85)		3085 (open-label) (CS Table 92)	
	Reslizumab N=245	Placebo N=243	Reslizumab N=232	Placebo N=232	Reslizumab N=~~571~~ 103	Placebo N=105	Reslizumab N=571	Placebo N=480
Asthma	97 (40)	127 (52)	67 (29)	118 (51)	16 (16)	20 (19)	159 (28)	145 (30)
Upper respiratory tract infection	39 (16)	32 (13)			5 (5)	3 (3)	57 (10)	51 (11)
Nasopharyngitis	28 (11)	33 (14)	45 (19)	56 (24)	6 (6)	4 (4)	81 (14)	69 (14)
Sinusitis	21 (9)	29 (12)					43 (8)	35 (7)
Headache	19 (8)	30 (12)	33 (14)	17 (7)	11 (11)	6 (6)	39 (7)	34 (7)
Influenza	18 (7)	23 (9)						
Bronchitis	13 (5)	24 (10)			2 (2)	5 (5)	29 (5)	33 (7)
Back pain	13 (5)	13 (5)	12 (5)	8 (3)				
Urinary tract infection	13 (5)	11 (5)	8 (3)	16 (7)			28 (5)	16 (3)
Oropharyngeal pain	13 (5)	8 (3)						
Rhinitis allergic	13 (5)	6 (2)					31 (5)	19 (4)
Nausea	12 (5)	10 (4)						
Cough	11 (4)	13 (5)						
Pharyngitis	10 (4)	13 (5)						
Dyspnoea	10 (4)	12 (5)						
Fatigue	6 (2)	11 (5)						
Dizziness	5 (2)	13 (5)						

Discontinuations due to adverse events

Three trials (~~*RES-05*~~ *Res-5*-0010, 3081 and 3084) reported patients discontinuing due to adverse events at 16±1 weeks and two (~~*3081*~~ *3082* and ~~*3084*~~ *3083*) ~~*to data*~~ at 52 weeks (Table 32). The proportion of patients that discontinued due to adverse events varied from 0.87% to 1.8% over 16±1 weeks, and from 2% to 4% over 52 weeks.

Table 32 Discontinuations due to adverse events up to 16±1 and 52 weeks

		Reslizumab versus placebo			
		16±1 weeks (CS Table 72)		52 weeks (CS Table 74)	
Trial	**Treatment arm**	**N**	**Discontinuations due to AE, % of patients**	**N**	**Discontinuations due to AE, % of patients**
Res-5-0010, (15 weeks)	Reslizumab	53	0	NR	NR
	Placebo	53	1.8	NR	NR
3081 (16 & 52 weeks)	Reslizumab	103	1.09	*NR*	*NR*
	Placebo	105	0	*NR*	*NR*
3084 (16 & 52 weeks)	Reslizumab	395	0.87	*NR*	*NR*
	Placebo	97	1.2	*NR*	*NR*
3082 (52 weeks)	*Reslizumab*	*NR*	*NR*	*243*	*2.0*
	Placebo	*NR*	*NR*	*241*	*3.0*
3083 (52 weeks)	*Reslizumab*	*NR*	*NR*	*230*	*3.0*
	Placebo	*NR*	*NR*	*227*	*4.0*

AE: adverse events; NR: not reported

The company conducted direct comparisons of discontinuations due to adverse events in reslizumab and placebo treated patients and the results are shown in Table 33. Differences between reslizumab and placebo were not statistically significant over either 16±1 weeks or 52 weeks. Fixed and random effects models gave identical results; no heterogeneity was detected by the I^2 test.

Table 33 Direct comparison meta-analysis: Discontinuation due to adverse events up to 16±1 and 52 weeks

	Odds ratio, reslizumab versus placebo (95% CI)	
	16±1 weeks (CS Table 73)	**52 weeks (CS Table 75)**
Fixed-effects model	0.83 (0.17, 4.16)	0.70 (0.33, 1.5)
Random-effects model	0.83 (0.17, 4.16)	0.70 (0.33, 1.5)

	Odds ratio, reslizumab versus placebo (95% CI)	
	16±1 weeks (CS Table 73)	**52 weeks (CS Table 75)**
P-value of the Cochran test	0.64	0.46
I^2	0%	0%

The CS states that results for this outcome are mean differences; however, they are odds ratios

Serious adverse events

Three trials (3081, 3084 and Res-5-0010) reported serious adverse events at 16±1 weeks and ~~T~~ two trials (3082 and 3083) reported serious adverse events at 52 weeks. The sample size reported in the CS for this outcome at 52 weeks is slightly smaller than the safety analysis set in both trials, but no explanation is provided. The proportion of patients with serious adverse events at ~~52 weeks~~ varied from 1.89% to 10.3% at 16±1 weeks and 8% to 14% at 52 weeks (Table 34).

Table 34 Serious adverse events up to 16±1 and 52 weeks

Trial	Treatment arm	Serious adverse event, % of patients		Source
		16±1 weeks	52 weeks	
3082	Reslizumab	Not reported	10.0 (n=243)	CS Tables 76 & 78
	Placebo	Not reported	14.0 (n=241)	
3083	Reslizumab	Not reported	8.0 (n=230)	
	Placebo	Not reported	10.0 (n=227)	
3081	Reslizumab	6.8 (n=103)	Not reported	
	Placebo	3.8 (n=105)	Not reported	
3084	Reslizumab	6.3 (n=395)	Not reported	
	Placebo	10.3 (n=97)	Not reported	
Res-5-0010	Reslizumab	3.80 (n=53)	Not reported	
	Placebo	1.89 (n=53)	Not reported	

The company conducted direct comparison meta-analysis of the proportion of patients with serious adverse events in the reslizumab and placebo groups and the results are shown in Table 35. The differences between the groups were not statistically significant. Fixed and random effects models gave identical results; no heterogeneity was detected by the I^2 test.

Table 35 Direct comparison meta-analysis: serious adverse events up to 16±1 and 52 weeks

	Odds ratio, reslizumab versus placebo (95% CI)		Source
	16±1 weeks	52 weeks	CS Tables 77 & 79
Fixed-effects model	0.82 (0.43 to 1.55)	0.71 (0.47 to 1.08)	
Random-effects model	0.82 (0.43 to 1.55)	0.71 (0.47 to 1.08)	

	Odds ratio, reslizumab versus placebo (95% CI)		Source
P-value of the Cochran test	*0.28*	0.76	
I^2	*22%*	0%	

The CS states that results for this outcome are mean differences; however, they are odds ratios

Discontinuations due to serious adverse events were not reported.

3.3.5 HRQoL (AQLQ and other outcomes)

AQLQ

Three trials reported changes in AQLQ scores over 16 weeks (Table 36). Two different sample sizes are reported for these trials in the CS: the sample sizes given in CS Tables 24, 34 and 48 (summarised here in Table 36) do not agree with those given in CS Table 63. The largest discrepancy is for trial 3081 where the numbers of reslizumab and placebo patients analysed were, respectively, n=99 and n=101 according to CS Table 48 but were n=91 and n=84 according to CS Table 63. All the sample sizes reported in the CS for this outcome are smaller than both the number randomised and the FAS for each trial. No explanation for the missing data is provided.

Improved asthma-related quality of life is indicated by higher AQLQ scores, and the scores consistently increased to a statistically significantly greater extent in the reslizumab group than the placebo group.

Table 36 AQLQ score: mean change from baseline at 16 weeks

Trial	Reslizumab	Placebo	Mean difference (95% CI)	Source
3082	1.03 (n=228)	0.87 (n=229)	0.24 (0.05, 0.43); p=0.0143	CS Table 24
3083	0.95 (n=213)	0.79 (n=216)	0.21 (0.03, 0.39); p=0.0259	CS Table 34
3081	1.14[a] (n=99)	0.78[a] (n=101)	0.36 (0.05, 0.67); p=0.0241	CS Table 48

[a] least squares mean

Direct comparison meta-analysis of AQLQ scores was conducted for the change to 16 weeks and also for the change to 52 weeks. The meta-analysis of the change to 52 weeks was based on two trials, 3082 and 3083 (Table 37), although the CS does not report the mean difference for each trial. Unlike the 16-weeks analysis, the 52-weeks analysis is reported to have been based on all randomised patients.

Table 37 AQLQ score: mean change from baseline at 52 weeks

Trial	Reslizumab	Placebo	Mean difference (95% CI)	Source
3082	1.30 (n=245)	1.01 (n=244)	Not reported	CS Table 65
3083	1.10 (n=232)	0.90 (n=232)	Not reported	CS Table 65

Results of the direct comparison meta-analysis of AQLQ scores for 16 and 52 weeks are given in Table 38. The pooled analysis indicates a statistically significantly greater increase in mean AQLQ scores, indicating better results in patients treated with reslizumab compared with placebo, both at 16 and 52 weeks. There were no differences between the random- and fixed-effects models. No heterogeneity was detected by the I^2 test (and therefore no forest plot was provided).

Table 38 Direct comparison meta-analysis: AQLQ score changes over 16 and 52 weeks

	Difference between means, reslizumab versus placebo (95% CI)		Source
	16 weeks	52 weeks	CS Tables 64 & 66
Fixed-effects model	0.24 (0.12 to 0.36)	0.33 (0.19 to 0.46)	
Random-effects model	0.24 (0.12 to 0.36)	0.33 (0.19 to 0.46)	
P-value of the Cochran test	0.77	0.51	
I^2	0%	0%	

Abbreviations: CI, confidence interval; AQLQ, Asthma Quality of Life Questionnaire.
A positive change from baseline indicates that reslizumab is better than placebo.
I^2 is based on the Q statistic from the Cochran test and is a measure of heterogeneity.

Other HRQoL outcomes: ASUI

The company did not meta-analyse any other HRQoL outcomes. However, the CS presents trial results for changes up to 16 weeks in the Asthma Symptom Utility Index (ASUI) from trials 3082, 3083 and 3081, and for completeness we have summarised these below in Table 39. The sample sizes reported in the CS for this outcome are smaller than both the number randomised and the FAS for all three trials, but no explanation is provided.

Improvement in asthma symptoms is indicated by an increase in ASUI scores. In all three trials the ASUI scores showed a greater increase in the reslizumab group than the placebo group, with the difference being statistically significant in each case.

Table 39 ASUI score: mean change from baseline at 16 weeks

Trial	Reslizumab	Placebo	Mean difference (95% CI)	Source
3082[a]	0.17[b] (n=238)	0.11[b] (n=238)	0.06 (0.03, 0.08); p<0.0001	CS Table 27
3083[a]	0.12[b] (n=227)	0.08[b] (n=224)	0.04 (0.01, 0.06); p=0.0037	CS Table 37
3081[a]	0.13[b] (n=101)	0.08[b] (n=103)	0.05 (0.01, 0.09); p=0.0160	CS Table 49

[a] change calculated as weighted average across 16 weeks
[b] least squares mean

AQLQ responder analysis results are presented in the CS for trial 3082 (week 52; CS section 4.7.1.4), trial 3083 (weeks 16 and 52; CS section 4.7.2.4) and trial 3081 (week 16; CS section 4.7.3.8). In each case the proportion of responders was [redacted] in the reslizumab-treated than the placebo group. However, the analysis is limited as it was not controlled for multiple testing and we are unclear whether it was planned or post-hoc. We note that the responder proportion in the placebo group was [redacted] (e.g. [redacted] in trial 3082 at 52 weeks) whilst by comparison the difference in responder rates between reslizumab and placebo groups was [redacted] (e.g. [redacted] responders in the reslizumab than the placebo group in trial 3082 at 52 weeks). Due to the limitations in the analysis [redacted] the AQLQ responder analysis results should be treated with caution.

3.3.6 Other supporting outcomes

The CS presents relatively extensive information on two outcomes which are not specified in the NICE scope: use of short-acting beta-agonists (SABA), and blood eosinophil concentrations. The company did not conduct any meta-analyses on these outcomes but we have summarised the trial results for these outcomes below for completeness.

The four company trials of reslizumab versus placebo provided information on changes in SABA use (Table 40). For all four trials the sample size reported in the CS for this outcome is smaller than the number randomised and, where trials defined it, the FAS.

There was a consistent tendency for use of SABA to be reduced more in the reslizumab groups than the placebo groups, except in trial 3084 which unlike the other trials included some patients with baseline eosinophil levels <400 per µL. However the difference was only statistically significant in trial 3081. According to clinical experts advising the ERG, decline in SABA use in

the placebo group is expected, as effects of trial inclusion and placebo are well known in asthma trials.

Table 40 SABA use: mean changes from baseline (puffs/day) at 16±1 weeks

Trial	Reslizumab	Placebo	Mean difference (95% CI)	Source
3082[a] *(LS mean)*	[redacted]	[redacted]	[redacted]	CS Table 28
3083[a] *(LS mean)*	[redacted]	[redacted]	[redacted]	CS Table 38
3081[a] *(LS mean)*	[redacted]	[redacted]	[redacted]	CS Table 50
3084[b] *(LS mean)*	[redacted]	[redacted]	[redacted]	CS Table 55

[a] change calculated as weighted average across 16 weeks
[b] change calculated at week 16; data are for total trial population which included patients with baseline eosinophils <400 and ≥400 per µL

Five trials reported changes from baseline in blood eosinophil concentrations at 16±1 weeks (Table 41) and two trials reported this outcome at 52 weeks (Table 42). For all the trials which reported this outcome, the sample size reported in the CS is smaller than both the number randomised and, where defined, the FAS.

The reduction in eosinophil concentrations was significantly larger in the reslizumab groups in all cases.

Table 41 Blood eosinophils: mean or median changes from baseline at 16±1 weeks

Trial	Reslizumab	Placebo	Mean difference (95% CI)	Source
3082[a] (LS mean)	[redacted]	[redacted]	[redacted]	CS Table 29
3083[a] (LS mean)	[redacted]	[redacted]	[redacted]	CS Table 39
3081[a] (LS mean)	[redacted]	[redacted]	[redacted]	CS Table 51
3084[c] (LS mean)	[redacted]	[redacted]	[redacted]	CS Table 55
Res-5-0010[d] (median)	[redacted]	[redacted]	[redacted]	Castro et al. [22]

LS: least squares
[a] change calculated as weighted average across 16 weeks
[b] typographic error in CS corrected by ERG
[c] change calculated at week 16; data are for total population with baseline eosinophils <400 per μL and ≥400 per μL
[d] change calculated at week 15

Table 42 Blood eosinophils: mean or median changes from baseline at 52 weeks

Trial	Reslizumab	Placebo	Mean difference (95% CI)	Source
3082[a b] (LS mean)	–582 (n=243) cells/ μL	–127 (n=241) cells/ μL	–455 (–491, –419); p<0.0001 cells/ μL	CS Table 29
3083[a] (LS mean)	–565 (n=230) cells/ μL	–76 (n=226) cells/ μL	–489 (–525, –453); p<0.0001 cells/ μL	CS Table 39

LS: least squares
[a] change calculated as weighted average across 52 weeks
[b] analysis not controlled for multiplicity

3.3.7 Sub-group analyses results

The NICE scope does not specify any specific subgroups for this appraisal. However, the CS refers to two subgroups which were analysed in the trials:

Subgroups according to baseline blood eosinophil concentration (trial 3084 only)
Asthma control, lung function and SABA use outcomes in trial 3084 were analysed for the total trial population and also separately for subgroups of patients who had baseline eosinophil counts <400 per μL or ≥400 per μL. We note that the ≥400 per μL subgroup is most relevant to the definition of elevated blood eosinophils, but sacrifices sample size compared to the total trial population. Subgroup results are reported for the changes from baseline in FEV1, FVC, ACQ score and SABA use. The mean increase in FEV1 was statistically significantly larger with reslizumab than with placebo only in the subgroup with ≥400 eosinophils per μL (i.e. there was no significant difference in the <400 per μL subgroup or the total trial population) (CS Table 54). The mean changes in FVC and in SABA use did not differ significantly between reslizumab and placebo in either of the subgroups or the total trial population (CS Table 55). The decline in ACQ score was significantly larger with reslizumab than with placebo *only* in the *≥400 eosinophils per μL subgroup and the* total trial population *(p=0.0457), but not in the <400 per μL*

~~subgroup~~ (CS Table 55). A limitation of these findings, however, according to the trial publication,[21] is that the trial was not powered statistically for these subgroup analyses.

'FEV1 analysis set' (trials 3082, 3083, 3081)
This refers to analysis of the change from baseline in FEV1 in a subset of patients who had a % predicted FEV1 at baseline of ≤85%, i.e. patients with more severe asthma. In trial 3082 the company conducted analyses "to" 16 weeks and "over" 16 weeks (for interpretation see section 3.1.6) and these gave different results (CS section 4.7.1.3): the first analysis gave a non-significant difference in the change from baseline of 0.07 L between reslizumab and placebo (p=0.0834), whilst the second analysis gave a statistically significant difference of 0.14 L (p<0.0001). In trial 3083 the same two analyses were conducted and both gave statistically significant differences favouring reslizumab over placebo (CS section 4.7.2.3): the difference in mean change "to" 16 weeks was 0.13 L (p=0.0040)whist the difference in change "over" 16 weeks was 0.11 L (p=0.0033). In trial 3081 only an analysis "over" 16 weeks is reported and this statistically significantly favoured reslizumab compared to placebo (CS section 4.7.3.2), with the difference in change from baseline being 0.17 L p=0.0066) (CS Table 43). As stated in the CS, a limitation of these findings is that the trials were not powered statistically for these subgroup analyses.

The CS (section 4.8) also mentions a subgroup analysis of CAE rates in adult patients at GINA steps 4 and 5 (i.e. excluding young people aged <18) which classified patients according to whether or not they were on oral corticosteroids at baseline. The data source appears to be from several pooled trials but this is not explicitly stated and the subgroup sizes are not reported in the CS. This analysis is not discussed in the current report.

3.4 Indirect treatment comparison results: reslizumab versus omalizumab

The CS reports an indirect treatment comparison (ITC) for seven outcomes. These are one lung function outcome (change in FEV1), one asthma control outcome (change in ACQ score), one HRQoL outcome (change in AQLQ score), two exacerbations outcomes (frequency of clinically significant exacerbations, and patient hospitalisations due to exacerbations), and two adverse events outcomes (discontinuations due to adverse events, and serious adverse events)

3.4.1 Asthma control

Change in ACQ score from baseline to 16±1 weeks

Five reslizumab trials and two omalizumab trials reported changes in the ACQ score from baseline to 16±1 weeks (Table 43). The omalizumab trials had different comparators (placebo and optimised asthma therapy) but the ITC Report does not discuss whether they were equivalent to BSC. One of the omalizumab trials (EXALT) was open-label.

Table 43 Trials included in the ITC for ACQ score change at 16±1 weeks

Reslizumab trials	Omalizumab trials	Source
3082, 3083, 3081, 3084 Res-5-0010	Garcia et al.[31] (comparator: placebo) EXALT[32] (comparator: optimised asthma therapy)	ITC Report Table 43

All trials were 16 weeks except Res-5-0010 (15 weeks)

Note that the sample sizes reported for this outcome in trials 3082 and 3083 in the ITC Report (ITC Report Table 14) are smaller than those reported for the direct comparison of the same outcome in the CS (CS Tables 25 & 35). No explanation for this discrepancy is provided.

A direct comparison was conducted for the two omalizumab trials (ITC Report Table 44). The following results were obtained for the difference between omalizumab and comparator groups in the ACQ score change from baseline at 16±1 weeks:

- Fixed-effects mean difference: ─0.55 (95% CI ─0.73, ─0.36)
- Random-effects mean difference: ─0.39 (95% CI ─0.84, 0.06)

The fixed-effects model but not the random-effects model indicates a significant difference between omalizumab and the comparator group in the change in the ACQ score. The ITC Report correctly points out that the fixed-effects model is not appropriate as there was significant statistical heterogeneity (I^2=87%; Cochran test p-value=0.0058). A forest plot in the ITC report (not reproduced here) shows marked heterogeneity in effect size between the two omalizumab trials (ITC Report Figure 9).

The company conducted a sensitivity analysis excluding one open-label trial (EXALT), leaving only the Garcia et al.[31] trial in the analysis (ITC Report Table 46). This gave a fixed-effects

mean difference of 0.00 (95% CI –0.43, 0.43), indicating no difference in ACQ score changes between omalizumab and the comparator.

The company conducted an ITC to compare reslizumab against omalizumab using the five reslizumab and two omalizumab trials, and also conducted a sensitivity analysis of the ITC excluding the open-label EXALT trial (Table 44). The company concluded that, based on the random-effects model, reslizumab is comparable to omalizumab in terms of change from baseline in ACQ score at 16±1 weeks (ITC Report section 3.5.3).

Table 44 ITC results for ACQ score change at 16 weeks

Analysis		Difference (95% CI)	Source
All trials	**Fixed-effects estimate**	0.30 (0.10, 0.55)	ITC Report Table 45
	Random-effects estimate	0.15 (–0.31, 0.61)	
Excluding 1 open-label omalizumab trial	**Fixed-effects estimate**	–0.24 (–0.68, 0.19)	ITC Report Table 47
	Random-effects estimate	Not reported	

Change in ACQ score from baseline to 52 weeks

The company could not conduct this analysis due to a lack of trials reporting this outcome.

3.4.2 Exacerbations

The company sought to identify omalizumab trials which provided comparable definitions of clinically significant exacerbations to those given in the reslizumab trials (ITC Report section 3.7). The process for selecting the omalizumab studies is not entirely clear. We are concerned that the company has applied their definitions of clinically significant exacerbations inconsistently to the trials, resulting in the inappropriate exclusion of some omalizumab trials. This view was corroborated by a clinical expert advising the ERG.

In the ITC Report, reslizumab trials identified “clinically significant exacerbations” as those that encompass both “moderate” and “severe” exacerbations consistent with the GINA and BTS SIGN guidelines. As such, only omalizumab trials reporting exacerbation definitions that can be classified as either moderate or severe according to these two guidelines were considered to be

comparable to reslizumab trials. The ITC Report classifies the exacerbation definitions in the trials as to whether they are equivalent to moderate or severe according to ATS/ERS and GINA/BTS definitions but then does not appear to use this classification when identifying which trials to exclude or include (ITC Report Table 55).

The company also defines clinically significant exacerbations as "events requiring the use of systemic corticosteroids and/or unscheduled visit to the hospital, the emergency department and the general practitioner." The trials listed in ITC Report Table 55 which have been excluded because the exacerbation definition "only considers the use of systemic corticosteroid" would appear to meet the company's definition of a clinically significant exacerbation.

Due to these inconsistencies it is unclear whether the ITC exacerbation outcome results summarised below are based on all relevant omalizumab trials.

Rates of clinically significant exacerbations

Three reslizumab trials and three omalizumab trials were identified by the company which they considered to be comparable in terms of how they defined clinically significant exacerbations (Table 45). The omalizumab trials had different comparators (placebo and optimised asthma therapy) but the ITC Report does not discuss whether these were equivalent to BSC.

Table 45 Trials included in the ITC for clinically significant exacerbations

Reslizumab trials	Omalizumab trials	Source
3082, 3083, Res-5-0010	Chanez et al.[33] (comparator: placebo) INNOVATE[34] (comparator: placebo) EXALT[32] (comparator: optimised asthma therapy)	ITC Report Table 55

NB: Res-5-0010 reported exacerbations over 15 weeks and INNOVATE over 28 weeks

A direct comparison of clinically significant exacerbation rates in the omalizumab trials is not provided in the ITC Report.

The Bayesian ITC analysis comparing clinically significant exacerbation rates in reslizumab and omalizumab trials produced deviance information criterion (DIC) values of 78.06 for the fixed-effects model and 78.81 for the random-effects model. The company selected the fixed-effects model based on this very small difference in the DIC. We caution that this is a not an

appropriate approach, since model fit is arguably less important than model plausibility,[26] and a random-effects model would appear more appropriate given that marked heterogeneity among the trials was detected by the company (ITC Report Figure 12). ~~*Unlike with the other outcomes where both fixed- and random-effects results are reported (where applicable), only the fixed-effects results have been given by the company for the ITC analysis of exacerbation rates*~~ *Results of the random-effects analysis are presented separately in ITC Report Appendix 12 and are not discussed by the company but we have provided them here for comparison* (Table 46).

The company conducted a sensitivity analysis by running the ITC without the open-label omalizumab study EXALT. This produced DIC values of 64.17 for the fixed-effects model and 65.61 for the random-effects model. The company ~~*again*~~ (inappropriately in our opinion) used the DIC to justify presenting only results for the fixed-effects analysis (Table 46).

Table 46 ITC ~~*fixed-effects*~~ model results for clinically significant exacerbations

Analysis	Comparison	Median hazard ratio (95% CrI)	Proba-bility	Source
All trials, *fixed effects analysis*	**Reslizumab vs placebo**	0.44 (0.35, 0.56)	100%	ITC Report Table 57
	Reslizumab vs omalizumab	0.80 (0.44, 1.44)	77%	
All trials, random effects analysis	***Reslizumab vs placebo***	*0.43 (0.17, 1.10)*	*97%*	*ITC Report Appendix 12*
	Reslizumab vs omalizumab	*0.18 (0.18, 2.82)*	*71%*	
Excluding 1 open-label omalizumab trial[a]	**Reslizumab vs placebo[a]**	0.44 (0.35, 0.56)	100%	ITC Report Table 59
	Reslizumab vs omalizumab	0.54 (0.26, 1.12)	95%	

CrI: credible interval

[a] ERG assumes this is a fixed-effects analysis – not stated explicitly in the CS

The fixed-effects ITC hazard ratio favours reslizumab over omalizumab in terms of having a lower rate of clinically significant exacerbations and this effect is strengthened in the sensitivity analysis limited to double-blind studies. The 'probability' in Table 46 refers to the Bayesian probability that reslizumab will perform better than omalizumab; a probability of 100% indicates reslizumab always performs better. *However, in the random-effects analysis the median hazard ratio for comparing the rate of clinically significant exacerbations between the reslizumab and placebo groups is considerably smaller (Table 46).*

~~*Whilst these results appear to convincingly demonstrate the benefit of reslizumab over omalizumab in reducing the overall rate of clinically significant exacerbations, we caution that the results are actually less certain because a random-effects analysis has not been presented.*~~

Number of patients hospitalised due to exacerbations

Only one reslizumab trial (Res-5-0010[22]) and one omalizumab trial (Busse et al. 2001[35]) were available for the ITC analysis of patients hospitalised due to exacerbations up to 16±4 weeks (CS Table 61). The company deemed this analysis not to be feasible due to the low numbers of events reported. In Res-5-0010, only one hospitalisation occurred, suggesting that the short duration of the trial (15 weeks) was inadequate for assessing hospitalisation rates.

Two reslizumab trials and two omalizumab trials reported the number of patients hospitalised due to exacerbations up to 52 weeks (Table 47). The omalizumab trials were both open-label.

Table 47 Trials included in the ITC for patients hospitalised due to exacerbations up to 52 weeks

Reslizumab trials	Omalizumab trials	Source
3082, 3083	Ayres et al.[36] (comparator: BSC) (open-label trial) Niven et al.[37] (comparator: BSC) (open-label trial)	ITC Report Table 62

The ITC Report presents the percentage of patients hospitalised due to exacerbations in each arm of the four trials (ITC Report Figure 14, not reproduced here) and this shows that the BSC arms of the omalizumab trials had higher hospitalisation rates than the placebo arms of the reslizumab trials.

Note that the ITC report describes the statistical results for this outcome as mean differences but they are odds ratios, as we have indicated below.

A direct comparison was conducted for the two omalizumab trials (ITC Report Table 63). The following results were obtained for the difference between omalizumab and BSC in the number of patients hospitalised due to exacerbations up to 52 weeks:

- Fixed-effects odds ratio: 1.03 (95% CI 0.52, 2.05)
- Random-effects odds ratio: 1.03 (95% CI 0.52, 2.05)

The odds ratios for the fixed-effects and random-effects models are identical and not significantly different from 1.0, meaning that omalizumab did not differ significantly from BSC in terms of the odds of patients being hospitalised due to exacerbations. Statistical heterogeneity was not detected (I^2=0%; Cochran test p-value=0.99).

The company conducted an ITC to compare reslizumab against omalizumab using the two reslizumab trials and two omalizumab trials (Table 48). The pooled odds ratios are identical for the fixed-effects and random-effects models and are not significantly different from 1.0, indicating no difference between reslizumab and omalizumab in the odds of experiencing hospitalisation due to exacerbations up to 52 weeks. However, as mentioned in the ITC Report, a limitation is that both of the omalizumab trials included in the analysis were open-label (ITC Report section 3.8.4).

Table 48 ITC results for patients hospitalised due to exacerbations up to 52 weeks

Analysis		Odds ratio (95% CI)	Source
All trials	**Fixed-effects estimate**	0.71 (0.26, 1.89)	ITC Report Table 64
	Random-effects estimate	0.71 (0.26, 1.89)	

3.4.3 Lung function

Change in FEV1 from baseline to 16±4 weeks

Five reslizumab and three omalizumab trials reported change in FEV1 at 16±4 weeks (Table 49). The omalizumab trials had different comparators but the ITC Report does not discuss whether they are all equivalent to BSC.

Table 49 Trials included in the ITC for FEV1 change at 16±4 weeks

Reslizumab trials	Omalizumab trials	Source
3082, 3083, 3081, 3084, Res-5-0010	Garcia et al.[31] (comparator: placebo) Hoshino et al.[38] (comparator: "conventional therapy") QUALITX[39] (comparator: "control group")	ITC Report Table 35

All trials were 16 weeks except Res-5-0010 (15 weeks) and QUALITX (20 weeks)

A direct comparison was conducted for the three omalizumab trials (ITC Report Table 36). The following results were obtained for the difference between omalizumab and comparator groups in the FEV1 change from baseline at 16±4 weeks:

- Fixed-effects mean difference: 0.12 L (95% CI 0.06, 0.18)
- Random-effects mean difference: 0.14 L (95% CI 0.05, 0.24)

These differences are significantly greater than zero, meaning that omalizumab was favoured over the pooled comparator groups. However, there was significant statistical heterogeneity (I^2=72%; Cochran test p-value=0.03), and the changes were less than the minimal clinically important change in FEV1 of 0.2 L (ITC Report section 3.4.1). The ITC Report mentions that there were important differences in the FEV1 changes from baseline among the comparator (placebo and/or BSC) arms of the trials which might explain this heterogeneity.

The company conducted a sensitivity analysis excluding two open-label trials, leaving only the Garcia et al.[31] trial in the direct comparison (ITC Report Table 38). This gave a fixed-effects mean difference of 0.25 L (95% CI 0.08, 0.42), favouring omalizumab over placebo for improving FEV1 in this single trial.

Despite the heterogeneity among the omalizumab trials indicated by the direct comparison, the company conducted an ITC to compare reslizumab against omalizumab using the five reslizumab and three omalizumab trials (Table 50). The results indicate a lack of clinically significant or statistically significant differences between reslizumab and omalizumab in the FEV1 change from baseline to 16±4 weeks.

Table 50 ITC results for FEV1 change at 16±4 weeks

Analysis		**Difference (95% CI)**	**Source**
All trials	**Fixed-effects estimate**	0.00 (–0.07, 0.08)	ITC Report Table 37
	Random-effects estimate	–0.01 (–0.13, 0.01)	
Excluding 2 open-label omalizumab trials	**Fixed-effects estimate**	–0.13 (–0.3, 0.04)	ITC Report Table 39
	Random-effects estimate	Not reported	

Change in FEV1 from baseline to 52 weeks

Only two reslizumab trials and one omalizumab trial reported change in FEV1 at 52 weeks (Table 51).

Table 51 Trials included in the ITC for FEV1 change at 52 weeks

Reslizumab trials	Omalizumab trials	Source
3082, 3083	Niven et al.[37] (comparator: BSC)	ITC Report Table 40

A direct comparison of omalizumab versus BSC based on the single trial by Niven et al.[37] gave a fixed-effects mean difference of 0.32 L (95% CI 0.30, 0.34) (ITC Report Table 41), indicating the improvement in FEV1 provided by omalizumab was clinically and statistically significantly better than BSC alone.

Indirect comparison of reslizumab versus omalizumab based on the two reslizumab trials and one omalizumab trial indicated that, over 52 weeks, FEV1 was improved statistically significantly more by omalizumab than by reslizumab (Table 52). However, the ITC Report comments that the difference (0.19 L) was less than that considered to be clinically important (0.2 L) (ITC Report section 3.4.4).

Table 52 ITC results for FEV1 change at 52 weeks

Analysis		Difference (95% CI)	Source
All trials	**Fixed-effects estimate**	─0.19 (─0.25, ─0.13)	ITC Report Table 42
	Random-effects estimate	Not reported	

3.4.4 Adverse events

Discontinuations due to adverse events up to 16 weeks

Three reslizumab trials and two omalizumab trials reported discontinuations due to adverse events up to 16 weeks (Table 53).

Table 53 Trials included in the ITC for discontinuations due to adverse events up to 16 weeks

Reslizumab trials	Omalizumab trials	Source
3081, 3084, Res-5-0010	Chanez et al.[33] (comparator: placebo) Ohta et al.[40] (comparator: placebo)	ITC Report Table 65

A direct comparison was conducted for the two omalizumab trials (ITC Report Table 66). Note that the ITC report describes the statistical results for this outcome as mean differences but they

are odds ratios, as we have indicated below. The following results were obtained for the difference between omalizumab and placebo groups in the number of patients hospitalised due to exacerbations up to 52 weeks:

- Fixed-effects odds ratio: 0.73 (95% CI 0.27, 2.03)
- Random-effects odds ratio: 0.73 (95% CI 0.27, 2.03)

The odds ratios for the fixed-effects and random-effects models are identical and not significantly different from 1.0, indicating no difference between omalizumab and placebo in the odds of experiencing discontinuations due to adverse events up to 16 weeks. Statistical heterogeneity was not detected (I^2=0%; Cochran test p-value=0.34).

The company conducted an ITC to compare reslizumab against omalizumab using the two reslizumab trials and two omalizumab trials (Table 54). The pooled odds ratios are identical for the fixed-effects and random-effects models and are not significantly different from 1.0, indicating no difference between reslizumab and omalizumab in the odds of experiencing discontinuations due to adverse events up to 16 weeks (ITC Report section 3.9.3).

Table 54 ITC results for discontinuations due to adverse events up to 16 weeks

Analysis		Odds ratio (95% CI)	Source
All trials	**Fixed-effects estimate**	1.13 (0.17, 7.62)	ITC Report Table 67
	Random-effects estimate	1.13 (0.17, 7.62)	

Discontinuations due to adverse events up to 52±4 weeks

Two reslizumab trials and one omalizumab trial reported discontinuations due to adverse events up to 52±4 weeks (Table 55).

Table 55 Trials included in the ITC for discontinuations due to adverse events up to 52±4 weeks

Reslizumab trials	Omalizumab trials	Source
3082, 3083	EXTRA[41] (comparator: placebo)	ITC Report Table 68

All trials were 52 weeks except EXTRA (48 weeks)

A direct comparison of omalizumab versus placebo based on the single EXTRA trial gave a fixed-effects odds ratio of 1.46 (0.67, 3.18) (ITC Report Table 69) which indicates that the odds

of experiencing discontinuations due to adverse events up to 52±4 weeks did not differ significantly between omalizumab and placebo.

The company conducted an ITC to compare reslizumab against omalizumab using the two reslizumab trials and one omalizumab trial (Table 56). The fixed-effects odds ratio did not differ significantly from 1.0, indicating no difference between reslizumab and omalizumab in the odds of experiencing discontinuation due to adverse events up to 52±4 weeks (ITC Report section 3.9.6).

Table 56 ITC results for discontinuations due to adverse events up to 52±4 weeks

Analysis		Odds ratio (95% CI)	Source
All trials	**Fixed-effects estimate**	0.48 (0.16, 1.43)	ITC Report Table 70
	Random-effects estimate	Not reported	

Serious adverse events up to 16 weeks

Three reslizumab trials and four omalizumab trials reported discontinuations due to adverse events up to 16 weeks (Table 57).

Table 57 Trials included in the ITC for serious adverse events up to 16 weeks

Reslizumab trials	Omalizumab trials	Source
3081, 3084, Res-5-0010	Garcia et al.[31] (comparator: placebo) Busse et al.[35] (comparator: placebo) Chanez et al.[33] (comparator: placebo) Ohta et al.[40] (comparator: placebo)	ITC Report Table 71

Note that the ITC report describes the statistical results for this outcome as mean differences but they are odds ratios, as we have indicated below. A direct comparison of omalizumab versus placebo based on the four omalizumab trials gave identical fixed-effects and random-effects odds ratios of 0.79 (95% CI 0.39, 1.59) (ITC Report Table 72), indicating that the odds of experiencing serious adverse events up to 16 weeks did not differ significantly between omalizumab and placebo. No statistical heterogeneity was detected (I^2=0; Cochran test p=0.51).

The company conducted an ITC to compare reslizumab against omalizumab using the three reslizumab trials and four omalizumab trials (Table 58). The fixed-effects and random-effects

odds ratios were identical and did not differ significantly from 1.0, indicating no difference between reslizumab and omalizumab in the odds of experiencing serious adverse events up to 16 weeks (ITC Report section 3.10.3).

Table 58 ITC results for serious adverse events up to 16 weeks

Analysis		Odds ratio (95% CI)	Source
All trials	**Fixed-effects estimate**	1.04 (0.4, 2.68)	ITC Report Table 73
	Random-effects estimate	1.04 (0.4, 2.68)	

Serious adverse events up to 52±4 weeks

Two reslizumab trials and two omalizumab trials reported discontinuations due to adverse events up to 52±4 weeks (Table 59). The trials had different comparators, placebo and BSC, and the trial by Ayres et al.[36] was open-label.

Table 59 Trials included in the ITC for serious adverse events up to 52±4 weeks

Reslizumab trials	Omalizumab trials	Source
3082, 3083	Ayres et al.[36] (comparator: BSC) EXTRA[41] (comparator: placebo)	ITC Report Table 74

All trials were 52 weeks except EXTRA (48 weeks)

A direct comparison of omalizumab versus placebo/BSC based on the two omalizumab trials gave identical fixed-effects and random-effects odds ratios of 1.00 (95% CI 0.69, 1.46) (ITC Report Table 75), indicating that the odds of experiencing serious adverse events up to 52±4 weeks did not differ significantly between omalizumab and placebo/BSC. No statistical heterogeneity was detected (I^2=0; Cochran test p=0.36).

Sensitivity analysis of the effect of excluding the open-label trial, i.e. basing the analysis only on the EXTRA trial, gave a fixed-effects odds ratio of 0.89 (95% CI 0.57, 1.40) which also indicated no statistically significant difference between omalizumab and placebo/BSC.

The company conducted an ITC to compare reslizumab against omalizumab using the two reslizumab trials and two omalizumab trials (Table 60). The fixed-effects and random-effects odds ratios were identical and did not differ significantly from 1.0, indicating no difference between reslizumab and omalizumab in the odds of experiencing serious adverse events up to

52±4 weeks. A sensitivity analysis in the ITC which excluded the open-label omalizumab trial also gave a non-significant odds ratio (Table 60) (ITC Report section 3.10.7).

Table 60 ITC results for serious adverse events up to 52±4 weeks

Analysis	Comparison	Odds ratio (95% CI)	Source
All trials	**Fixed-effects model**	0.71 (0.4, 1.24)	ITC Report Table 76
	Random-effects model	0.71 (0.4, 1.24)	
Excluding 1 open-label omalizumab trial[a]	**Fixed-effects model**	0.80 (0.43, 1.48)	ITC Report Table 78
	Random-effects model	Not reported	

[a] ITC Report Table 78 incorrectly states the EXALT trial was excluded (the excluded trial was Ayres et al.[36]).

3.4.5 HRQoL

Change in AQLQ score from baseline to 16±4 weeks

~~Four~~ Three reslizumab trials and one omalizumab trial reported changes in AQLQ score from baseline to 16±4 weeks (Table 61). The omalizumab trial (QUALITX) had a comparator described as a 'control group' but the ITC Report does not discuss whether this is equivalent to BSC.

Table 61 Trials included in the ITC for AQLQ score change at 16±4 weeks

Reslizumab trials	Omalizumab trials	Source
3082, 3083, 3081 ~~Res-5-0010~~	QUALITX[39] (comparator: "control group")[a]	ITC Report Table 48

All trials were 16 weeks except Res-5-0010 (15 weeks) and QUALITX (20 weeks)
[a] ITC Report incorrectly states that the QUALITX comparator was a placebo (ITC Report Table 49)

Note that the sample sizes reported for this outcome in trials 3082, 3083 and 3081 in the ITC Report (ITC Report Table 16) are smaller than those reported for the direct comparison of the same outcome in the CS (CS Tables 24, 34, 48). No explanation for this discrepancy is provided.

The ITC Report presents the changes from baseline in each arm of four of the trials ~~(excluding Res-5-0010)~~ (ITC Report Figure 10, not reproduced here), which illustrate that both arms in each of the trials 3082, 3083 and 3081 achieved a clinically significant improvement in the

AQLQ score (i.e. at least 0.5 points) from baseline to 16±4 weeks. However, in the QUALITX trial of omalizumab versus a control group (which the ITC Report incorrectly labels as placebo), only the omalizumab arm achieved a clinically significant improvement from baseline in the AQLQ score.

A direct comparison of omalizumab versus the control group based on the single QUALITX trial gave a fixed-effects mean difference of 0.80 (95% CI 0.47, 1.13) (ITC Report Table 49), indicating the improvement in AQLQ score provided by omalizumab was statistically significantly better than the control group.

The company conducted an ITC to compare reslizumab against omalizumab using the ~~*four*~~ *three* reslizumab trials and one omalizumab trial (Table 62). The company concluded that the results of the ITC were statistically significant but the ITC Report does not comment on the fact that the difference favours omalizumab over reslizumab for improving the AQLQ score. However, as acknowledged in the ITC Report, the single included omalizumab trial was open-label, and the impact on the analysis results of excluding open-label studies could not be explored (ITC Report section 3.6.3).

Table 62 ITC results for AQLQ score change at 16±4 weeks

Analysis		**Difference (95% CI)**	**Source**
All trials	**Fixed-effects estimate**	–0.56 (–0.92, –0.20)	ITC Report Table 50
	Random-effects estimate	Not reported	

Change in AQLQ score from baseline to 52±4 weeks

Two reslizumab trials and one omalizumab trial reported change in AQLQ score from baseline to 52±4 weeks (Table 63).

Table 63 Trials included in the ITC for AQLQ score change at 52±4 weeks

Reslizumab trials	**Omalizumab trials**	**Source**
3082, 3083	EXTRA[41] (comparator: placebo)	ITC Report Table 51

All trials were 52 weeks except EXTRA (48 weeks)

The ITC Report presents the changes from baseline in each arm of the three trials (ITC Report Figure 11, not reproduced here) which illustrate that both arms in each trial achieved a clinically

significant improvement in the AQLQ score (i.e. at least 0.5 points) from baseline to 52±4 weeks.

A direct comparison of omalizumab versus placebo based on the single EXTRA trial gave a fixed-effects mean difference of 0.23 (95% CI 0.07, 0.39) (ITC Report Table 52), indicating the improvement in AQLQ score provided by omalizumab was statistically significantly better than the placebo group.

The company conducted an ITC to compare reslizumab against omalizumab using the two reslizumab trials and one omalizumab trial (Table 64). Results of the ITC were not statistically significant for the AQLQ score change to 52±4 weeks (ITC Report section 3.6.6).

Table 64 ITC results for AQLQ score change at 52±4 weeks

Analysis		**Difference (95% CI)**	**Source**
All trials	**Fixed-effects estimate**	0.10 (−0.11, 0.31)	ITC Report Table 53
	Random-effects estimate	Not reported	

3.5 Summary of clinical effectiveness evidence

3.5.1 Direct comparison of reslizumab against placebo

Direct comparison meta-analysis

The direct comparison meta-analysis based on data from the five included RCTs, where available, showed reslizumab was favoured statistically significantly over placebo for:

- Asthma control (ACQ score) change at 16 weeks (except not significant in trial 3084 which included some patients with blood eosinophil counts <400 per µL) (not analysed at 52 weeks);
- Rates of clinically significant exacerbations;
- Lung function: FEV1 change at 16 and 52 weeks;
- HRQoL: AQLQ change at 16 and 52 weeks

The direct comparison meta-analysis showed that reslizumab was not significantly different to placebo for:

- Rates of exacerbations requiring hospital and/or emergency room visits
- Rates of discontinuation due to adverse events up to 16 and 52 weeks
- Serious adverse events up to 52 weeks (16 weeks not analysed)

Direct comparison outcomes not meta-analysed

For outcomes which were reported in the CS but not meta-analysed, consistent results across the individual trials suggested that reslizumab was favoured over placebo for:

- Rates of clinically significant exacerbations requiring systemic corticosteroids over ≥3 days;
- Rates of clinically significant exacerbations requiring oral corticosteroids over ≥3 days;
- The probability of experiencing a CSE over 52 weeks;
- Lung function: %predicted FEV1 change at 16 and 52 weeks;
- Lung function: FVC change at 16 and 52 weeks (except not significant in trial 3084);
- HRQoL: ASUI score change at 16 weeks (52 weeks not analysed);
- Blood eosinophil concentrations at 16 and 52 weeks.

SABA use was decreased more in reslizumab than placebo patients in most trials but only in one trial was the difference statistically significant.

For outcomes which were reported in the CS but not meta-analysed, consistent results across the individual trials suggested that reslizumab was not significantly different to placebo for:

- The proportion of patients requiring hospitalisation due to exacerbations (although the number of events was relatively low);
- Lung function: $FEF_{25-75\%}$ change at 16 weeks (not analysed at 52 weeks).

Reslizumab appears to have a relatively good safety profile. Adverse events based on the open-label study 3085 showed that generally, placebo-treated patients had a slightly higher proportion of adverse events than reslizumab-treated patients, or the proportions in both groups were similar. Separate data for patients with continuous reslizumab treatment and those previously treatment naïve were not reported and it is unclear if this may have had an impact on the long-

term adverse event rates of reslizumab. Only one death occurred among the five trials (in the placebo group of trial 3082).

3.5.2 ITC of reslizumab against omalizumab

Asthma control (change in ACQ score) did not differ between reslizumab and omalizumab, and a sensitivity analysis including only double-blind omalizumab trials gave the same result.

The rate of CSE was significantly lower for reslizumab than omalizumab, and a sensitivity analysis including only double-blind omalizumab trials gave the same result. However, this was based only on a fixed-effects analysis whereas a random-effects model would have been more appropriate.

The frequency of hospitalisations due to exacerbations (not analysed at 16 weeks) did not differ between reslizumab and omalizumab at 52 weeks. However, only open-label omalizumab trials were available.

Lung function, assessed by change in FEV1, did not differ between reslizumab and omalizumab at 16 weeks but at 52 weeks was statistically significantly (and almost clinically significantly) better in omalizumab treated than reslizumab treated patients.

Both the rate of discontinuations due to adverse events and the frequency of serious adverse did not differ significantly between reslizumab and omalizumab treated patients.

HRQoL as assessed by the change in AQLQ, statistically favoured omalizumab over reslizumab at 16 weeks, but did not differ between reslizumab and omalizumab at 52 weeks.

3.5.3 Strengths and limitations of the clinical effectiveness evidence

Strengths

- The CS and ITC report are generally well structured and clearly presented.
- All relevant studies appear to have been located by the company.

- With the exception of trial Res-5-0010, the included trials are described clearly and in detail.
- The included trials are of generally high quality.

Limitations

- The trials had relatively short duration (52 weeks) considering the chronic nature of severe asthma; trial Res-5-0010 had a duration of only 15 weeks.
- Not all available lung function and ~~AQLQ~~ HRQoL outcomes were included in the direct comparison meta-analysis and ITC and there is lack of clarity in the CS and ITC report over the rationale for selecting some outcomes: feasibility assessments were incorrectly reported and poorly explained. In particular, inconsistent application of definitions of clinically significant exacerbations may have resulted in some omalizumab trials being excluded unnecessarily from the ITC.
- ~~The ITC analysis for change in AQLQ at 16 weeks included a reslizumab trial (Res-5-0010) which was not included in the direct comparison meta-analysis for the same outcome, and the reason for this is unclear.~~
- For most outcomes the sample sizes are smaller than the number of patients randomised and, wehre defined, also smaller than the FAS; no explanation is provided in the CS for missing data.
- The company has conducted more statistical tests than necessary which might increase the risk of type I errors. It is unclear why two different analyses for changes from baseline were conducted; the company does not specify which is the preferred analysis; and the analyses are not consistently reported across all outcomes.
- Trial 3084 included patients with a wider range of baseline blood eosinophil counts than in the other trials. The trial publication indicates 80% of the trial population had blood eosinophils <400 per µL. A subgroup of patients with counts ≥400 per µL would be most consistent with the other trials but at the expense of sample size. Sensitivity analyses to check the impact of the different patient subgroups in this trial were not conducted.
- Due to lack of relevant trials, the ITC is based on an assumption that the effectiveness of omalizumab in patients with elevated blood eosinophils is the same as that in patients with IgE-mediated asthma; however, the evidence for or against this is not discussed.
- For the ITC the company has assumed that placebo is comparable to BSC but no explanation is provided. Some of the omalizumab trials included in the ITC had

comparator groups which were not described as placebo or BSC but the company has not mentioned or discussed this.

- The company did not adequately assess the homogeneity of trials before including them in the ITC; the ERG agrees that for many variables the trials appear broadly homogeneous, but we note differences in exacerbation history which suggest that patients in omalizumab trials had more severe asthma than those in reslizumab trials.
- ~~*In the ITC analysis of exacerbation rates the company inappropriately used only a fixed-effects analysis; the results for this outcome might not reflect true effects.*~~
- The results of the ITC do not directly inform the company's health economic analysis.

4 COST EFFECTIVENESS

4.1 Overview of the company's economic evaluation

The company's submission to NICE includes:

i) a review of published economic evaluations of pharmacological interventions for severe eosinophilic asthma.

ii) a report of an economic evaluation undertaken for the NICE STA process. The cost effectiveness of reslizumab is compared with best standard of care and to omalizumab for patients with severe eosinophilic asthma.

4.2 Company's review of published economic evaluations

A systematic search of the literature was conducted by the manufacturer to identify economic evaluations, outcomes, and data related to the treatment of asthma patients. This search included components designed to identify HRQoL and cost data in addition to full economic evaluations published as of April 4, 2016 (the search date was not explicitly stated). MEDLINE, MEDLINE In-process, Embase, and EconLit were searched to identify information resources published after 2006. No justification for the choice of a cut-off date of 2006 was provided. No searches were conducted using the NHS Economic Evaluation Database or the HTA database, two databases commonly used for cost-effectiveness evidence searches. In addition to excluding randomised controlled trials, studies that did not present UK-based economic evaluations were excluded. This exclusion was not listed in the CS, but was provided in a supplementary report describing the systematic review of economic evidence,[42] which hereafter

is referred to as the Amaris SLR Report. The company reports their search strategy in CS Appendix 6.

Additional searches were conducted to identify conference presentations at meetings of:

- European Respiratory Society (ERS)
- American Thoracic Society (ATS)
- British Thoracic Society (BTS)
- American College of Chest Physicians (CHEST)
- The American Academy of Allergy, Asthma and Immunology (AAAAI)

A clinical expert advising the ERG suggested that the company should also have searched the International Severe Asthma Forum (ISAF) and the European Academy of Allergy and Clinical Immunology (EAACI).

Table 65 Inclusion and exclusion criteria for the systematic reviews of cost-effectiveness and HRQoL studies

	Inclusion criteria	Exclusion criteria
Population	• Severe asthma • Adults	• Non-human • Not severe asthma • Not including adults, or mixed population of adults and children • Mixed asthma populations (e.g. moderate and severe)
Intervention	All asthma therapies	
Comparators	All asthma therapies	
Outcomes	The outcome measures to be considered for the economic evaluation and QoL include but are not limited to: • Costs and resource use • Utilities • Modelled health states • Other economic outcomes • Patients utility scores and QoL data	Not including at least one outcome of interest based on inclusion criteria
Study design	Study type of interest: • Health economic evaluation • Model-based cost-effectiveness studies • Population-based study	RCTs Cost-effectiveness studies based on observational data Non-UK economic evaluations

	Inclusion criteria	Exclusion criteria
Language restrictions	English	Any language other than English

Adapted from CS Table 98, p.178; and Amaris Systematic Literature Review report[42]

In addition to the searches of conference websites, a hand search was conducted for health technology assessments on the National Institute for Health and Care Excellence (NICE website). See Section 3.1 of this report for the ERG critique of the search strategy. Additionally, whilst the NHS Economic Evaluation Database (NHS EED) is no longer being updated, it does contain references until December 2014 for economic evaluations, and therefore may contain relevant studies that may have been missed by the grey literature searches.

Screening was conducted by two independent investigators at both title and abstract and full text screening stages, any disagreements were settled through consensus with a third investigator. In order for a study to be included, it had to meet all inclusion criteria and none of the exclusion criteria (Table 65). For cost-effectiveness studies, the study design was required to be a UK based economic model; whilst for HRQoL studies observational studies were required. The inclusion and exclusion criteria for the systematic review of cost-effectiveness and the systematic review of HRQoL studies are reported in Table 65.

Inclusion and exclusion criteria reported in CS Table 98 did not include all criteria listed in the Amaris SLR Report, and the intervention field in CS Table 98 incorrectly requires all studies have reslizumab as the intervention. We have corrected errors in CS Table 98 and incorporated inclusion and exclusion criteria from the Amaris SLR Report in Table 65.

Figure 5 reproduces the company's flow diagram (CS Figure 40, page 179) for the systematic review of economic evaluations, HRQoL studies and resource use studies.

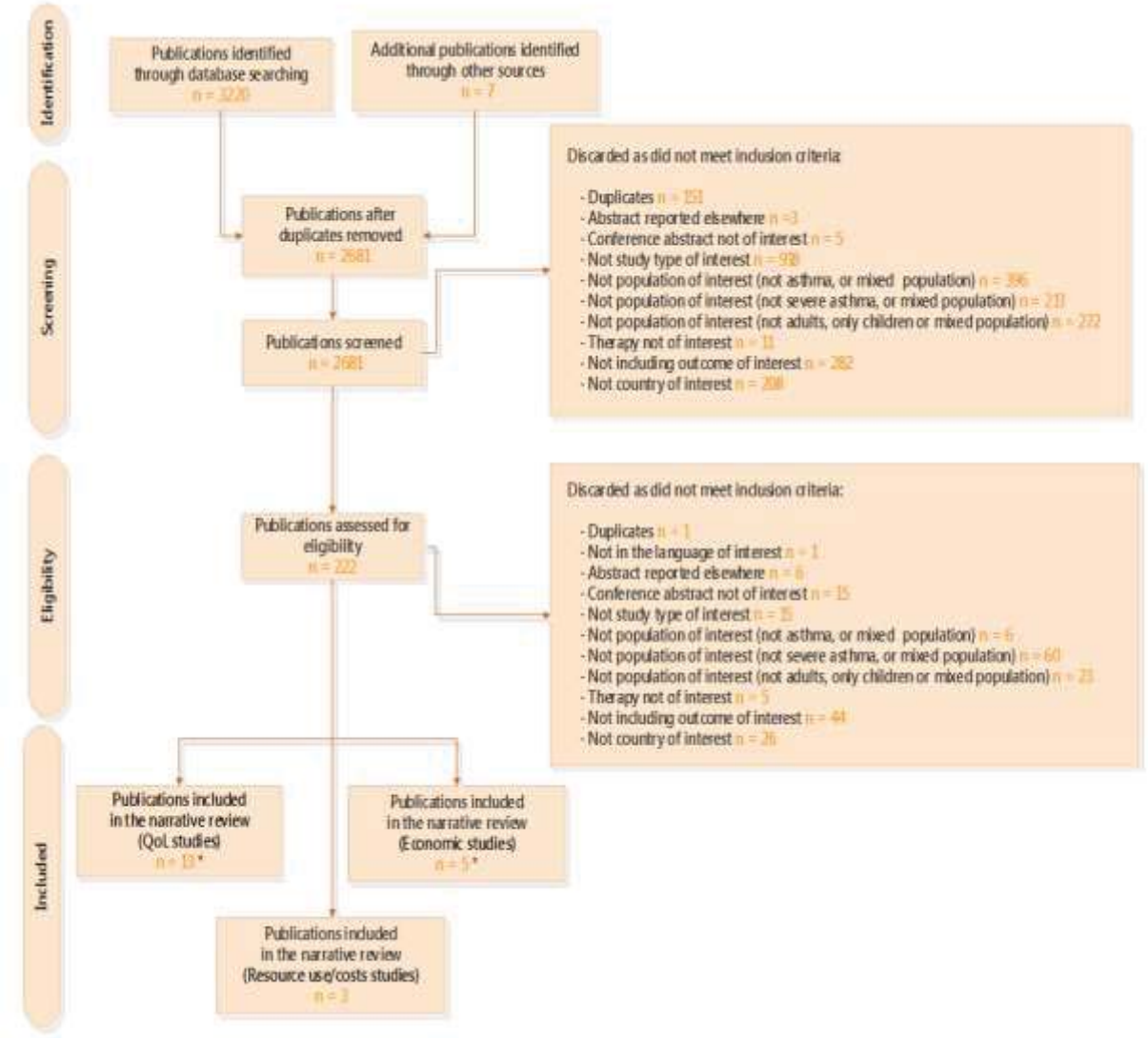


Figure 5 Flow diagram for the review of cost-effectiveness, HRQoL and healthcare resource use evidence

The systematic review identified 2,681 titles and abstracts, including 7 references identified through grey literature searches. Of the references identified, ~~2,661~~ 2,660 were excluded. The primary reasons for exclusion were “not population of interest” (970 references), “not study type of interest” (933 references), “not including outcome of interest” (326 references), and “not country of interest” (234 references). The “not population of interest” exclusion criterion was broken down into three categories: “not asthma or mixed severity population” (402 references); “not severe asthma or mixed severity population” (273 references); and “not adults, only children or mixed population” (295 references). In total, 13 HRQoL studies, three cost studies and five economic evaluation studies were included, resulting in 19 studies, in total being

identified (studies by Willson and colleagues and Thomson and colleagues[43, 44] were identified in two searches).

The CS reports that five cost-effectiveness studies were included in the systematic review of economic evaluations. These studies are summarised in Table 66 (adapted from CS Table 99).

Table 66 Summary of included cost-effectiveness studies

Study	Summary of model	Interventions	Patient population
Faria et al. 2014 (Adapted analysis of Norman et al.)[45]	Markov model	Omalizumab, BSC	Patients uncontrolled at GINA Step 4 and in the process of moving up to GINA Step 5, and patients controlled at Step 5 whose asthma would be uncontrolled if they were on Step 4 therapy, presented separately by age (adults and adolescents aged over 12 years and children aged 6–11 years).
Faria et al.2013[46]	Markov model	Omalizumab, BSC	Patients with severe asthma
Norman et al. 2013[47]	Markov model	Omalizumab, BSC	Adults and adolescents (greater than 12 years old) with severe uncontrolled asthma)
Willson et al. 2014[44]	Markov model	Teotropium bromide, BSC	The "PrimoTinA-asthma" clinical trials recruited asthma patients who were poorly controlled, confirmed by an ACQ-7 score ≥1.5 despite usual care comprising at least a high-dose ICS/LABA. Patients were also assumed to receive high-dose ICS/LABA as controller therapy.
Mepolizumab NICE technology appraisal[48]	Markov model	Mepolizumab, omalizumab, BSC	Adults with severe refractory eosinophilic asthma with a blood eosinophil count of ≥150 cells/μL at initiation of treatment; and ≥4 exacerbations in the previous year or dependency on maintenance OCS

All HRQoL and cost studies underwent quality assessment by the company using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.[49] Economic evaluations were quality assessed by the company using the checklist for economic evaluations in the *Developing NICE guidelines: the manual* publication.[50]

Limitations of the company's systematic reviews

Consultation with clinical experts indicated that there was no fundamental reason to believe that asthma symptoms or populations would be significantly different between different countries,

which weakens any justification for limiting economic evaluations to the UK. We ran some targeted searches to identify whether some studies may have been missed due to the company's exclusion criteria. In the CRD NHS EED and HTA databases we used the search term "severe asthma," and imposed no limitations on mixed populations, country of origin, or study design (non-UK models and RCTs were allowed). We limited studies to those published in the last 15 years with adult populations. This search identified four economic evaluations not identified by the company's searches: Brown and colleagues,[51] Dewilde and colleagues,[52] Gerzeli and colleagues,[53] and Morishima and colleagues.[54] Brown and colleagues, Dewilde and colleagues, and Morishima and colleagues were omalizumab economic evaluations in patients with severe asthma.[51, 52, 54] Gerzeli and colleagues evaluated the cost-effectiveness of beclomethasone/formoterol versus fluticasone propionate/salmeterol in patients with moderate to severe asthma.

In addition to the limitations of the company's systematic reviews noted above, the systematic reviews of HRQoL and resource use/cost studies did not include RCTs, which had the effect of excluding the pivotal reslizumab RCTs from consideration in the HRQoL review.[19]

It is unclear whether any of the mixed population studies contained data on relevant subgroups, so it is possible that relevant data and analyses were excluded from consideration. Given that there were hundreds of studies excluded for this reason, it was not feasible for the ERG to assess the relevance of these studies. It is also unclear why economic evaluations and HRQoL data from outside the UK were not considered relevant. It is understandable to omit resource use and cost data as these data are often healthcare system dependent, but HRQoL data are often applicable across countries and economic models are frequently adaptable to multiple settings.

4.3 Critical appraisal of the company's submitted economic evaluation

The following sections outline the ERG critical appraisal of the company's submitted economic evaluation.

4.3.1 NICE reference case

We have used the NICE reference case requirements to critically appraise the company's submitted economic evaluation, as shown in Table 67.

Table 67 NICE reference case requirements

NICE reference case requirements:	Included in submission	Comment
Decision problem: As per the scope developed by NICE	Yes	
Comparator: As listed in the scope developed by NICE	Yes	
Perspective on costs: NHS and PSS	Yes	
Evidence on resource use and costs: Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes	
Perspective on outcomes: All direct health effects, whether for patients or, when relevant, carers	Yes	
Type of economic evaluation: Cost utility analysis with fully incremental analysis	Yes	
Synthesis of evidence on outcomes: Based on a systematic review	Yes	Inclusion/exclusion criteria for systematic review of cost-effectiveness, HRQoL and costs reported in section 3.1
Time horizon: Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes	
Measuring and valuing health effects: Health effect should be expressed in QALYs. The EQ-5D is the preferred measure of health related quality of life.	Yes	HRQoL data were expressed in QALYs using EQ-5D-3L. Details of health effect measurement are reported in Section 0.
Source of data for measurement of health related quality of life: Reported directly by patients and/or carers.	Yes	HRQoL data were derived from two studies that used data reported directly by patients.
Source of preference data: Representative sample of the UK population	Yes	Valuation used the UK valuation set for EQ-5D-3L.
Equity considerations: An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	Yes	
Discount rate: 3.5% p.a. for costs and health effects	Yes	

Overall, the company has adhered to the recommendations of the NICE reference case.

4.3.2 Model Structure

The company constructed a Markov cohort model in Microsoft Excel to compare patients treated with reslizumab with those treated with omalizumab and best standard of care (BSC). A schematic of this model is provided in Figure 6. The model uses four week cycles in line with treatment cycles and a lifetime horizon (60 years). The analyses were conducted from the NHS

and PSS perspective, with discounting for costs and health benefits at 3.5% per year. Half-cycle correction was not included in the model.

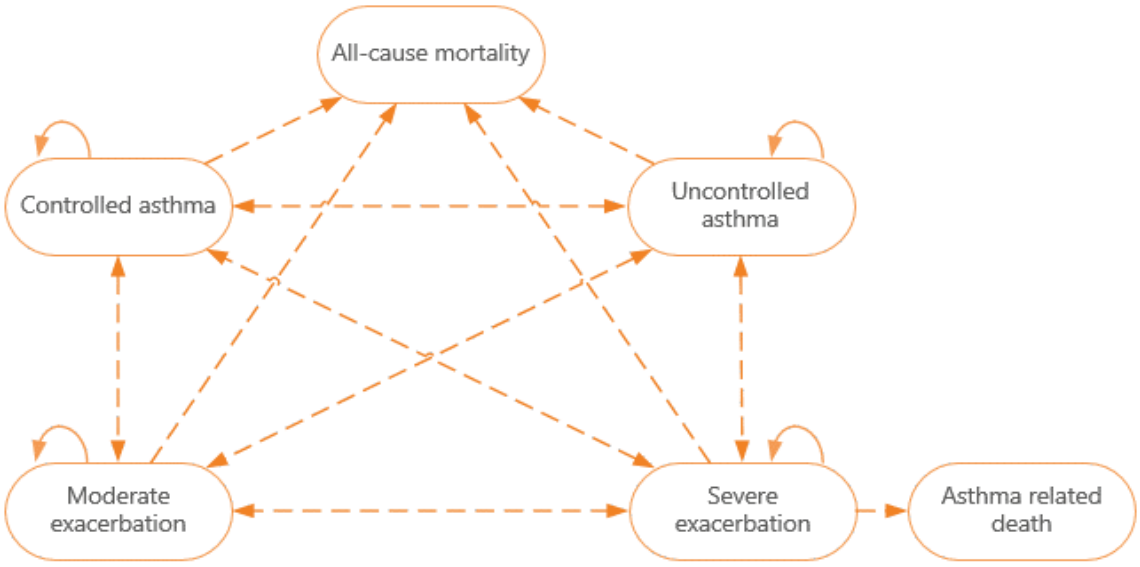


Figure 6 Schematic of company's model structure

The model is comprised of six mutually exclusive health states: Controlled asthma, uncontrolled asthma, moderate exacerbation, severe exacerbation, asthma-related death and all-cause mortality. It is assumed that patients can only die of asthma-related death having suffered a severe exacerbation. Patients enter the model in the uncontrolled asthma health state. Patients then transition between health states according to the transition probabilities (described in section 4.3.5).

The company states that the controlled and uncontrolled health states were defined based on the ACQ score in line with the BTS/SIGN guidelines,[5] where patients are classed as having uncontrolled asthma if their ACQ score is ≥1.5. The severity of exacerbation is defined according to the ERS/ATS guidelines,[9] as advised by their clinical experts, where a moderate exacerbation is defined to be associated with one or more of the following events: deterioration of symptoms; deterioration in lung function; increased rescue bronchodilator use but not severe enough to require additional use of systemic corticosteroids. A severe exacerbation is defined as an exacerbation requiring the use of additional systemic steroids.

In the model, patients treated with omalizumab are subject to a response rule at 16 weeks, based upon their treatment response, in line with the omalizumab SmPC.[55] In a similar way,

patients treated with reslizumab are assessed for response at [redacted] and the company states that this time-point was chosen because it represents the time by which improvements in asthma impairment can be measured in most patients based on the results of the Phase 3 trials. The assessment of treatment response is calculated using

‘[redacted]

‘[redacted]

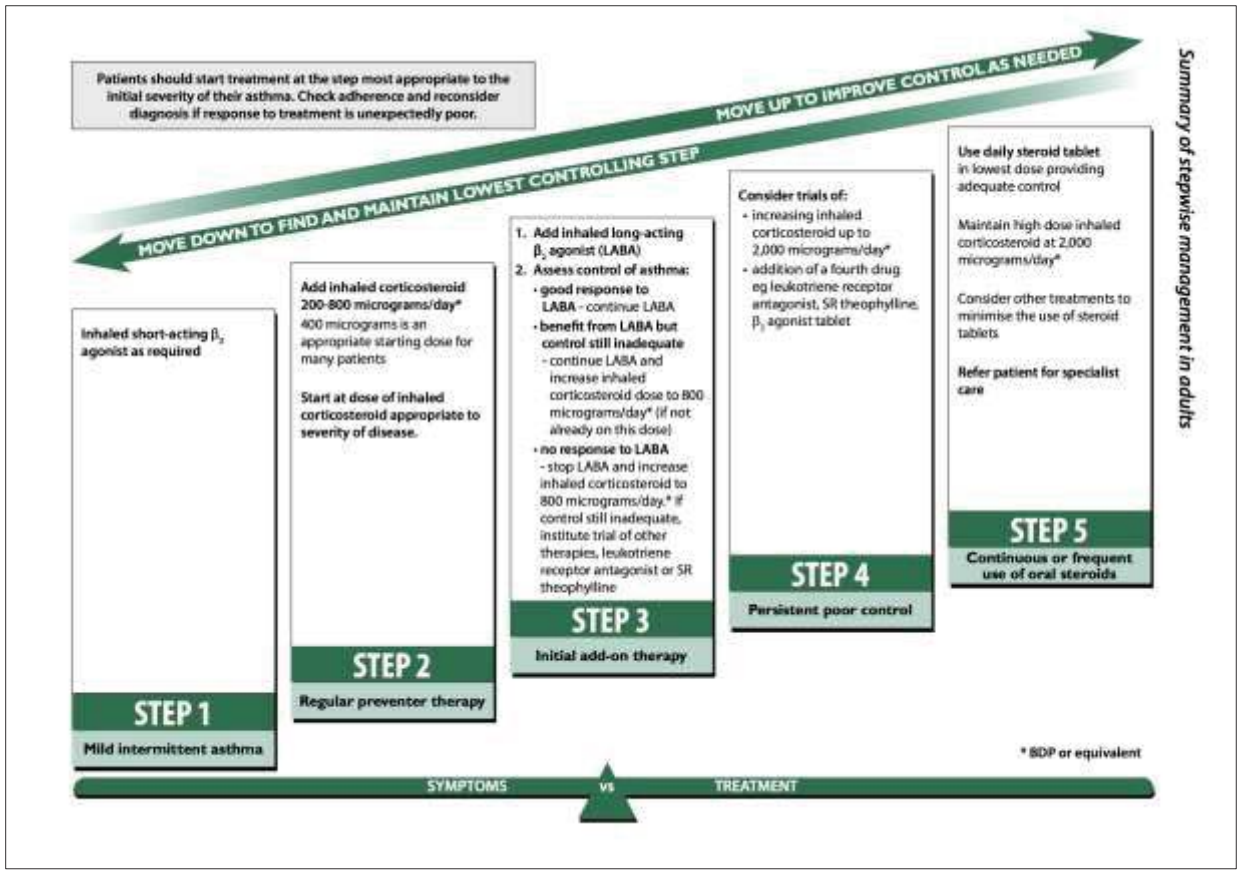
In the model, patients identified as non-responders transfer to the BSC treatment arm and then observe the BSC transition probabilities and costs for the remainder of the time horizon. Other patients (responders and those with an undetermined response status) are assumed to continue treatment beyond 16 weeks. In the model, patients are assumed to be assessed every year in line with the reslizumab SmPC. Patients who remain in the uncontrolled or exacerbation health states for one year will discontinue treatment. The company states that this assumption was validated by a panel of UK clinical experts. Patients treated with omalizumab follow the same discontinuation rules.

The company does not provide a rationale for the choice of model structure. The ERG considers the company’s model structure to be appropriate. We note that it differs from the structure used in previous technology appraisals for omalizumab[12] and mepolizumab.[56] Further, other previous published models for severe asthma have used slightly different model structures. The technology appraisal for omalizumab uses states for ‘day to day asthma symptoms’ (on either omalizumab or standard therapy), rather than uncontrolled and controlled health states. The technology appraisal for mepolizumab was based on a treatment model with health states for on-treatment pre-assessment, on-treatment post-assessment and off-treatment and death.

4.3.3 Population

The population defined in the NICE scope is adults with asthma and elevated blood eosinophils inadequately controlled by inhaled corticosteroids. This population is considered equivalent to

patients at Steps 4 and 5 of the BTS/SIGN and GINA treatment pathway (Figure 7).[5] Patient characteristics in the different arms of the pivotal trials used in this assessment were considered similar and well balanced, with a mean age from 43.0 years (trial 3081) to 47.5 years (trial 3083) and with more females enrolled in each trial than males (see section 3.1.3.2). The patient population considered for the company base case analysis was adult patients with asthma and elevated blood eosinophils aged 46.8 years with 63% females, at GINA Steps 4 and 5, who had experienced at least three exacerbations in the preceding year. It is not clear from the NICE scope how "elevated blood eosinophils" is defined in clinical practice, and the scope does not specify the number of exacerbations experienced in the preceding year. However, a clinical expert advising the ERG agreed that the threshold of ≥400 cells/μL for elevated blood eosinophils, and the distinction of ≥3 exacerbations employed by the company are reasonable. We also note that the second Appraisal Consultation Document for mepolizumab (June 2016) stated that the committee concluded for that appraisal that a blood eosinophil count of ≥300 cells/μL (ACD2 4.4, page 28) and ≥4 exacerbations in the previous year (ACD2 4.5, page 28) were appropriate criteria to define the population of interest. For comparison, the marketing authorisation for mepolizumab ("severe refractory eosinophilc asthma in adults") is different to the marketing authorisation for reslizumab ("adult patients with severe eosinophilic asthma inadequately controlled despite high-dose ICS plus another medicinal product for maintenance treatment").



Source: SIGN 141 British guideline on the management of asthma

Figure 7 Stepwise management of adults from SIGN/BTS guidelines

4.3.4 Interventions and comparators

Intervention: Add-on reslizumab

The intervention therapy is reslizumab, an intravenously administered infusion, as an add-on therapy to BSC. Reslizumab is a monoclonal anti-IL-5 antibody, indicated for adult patients with severe eosinophilic asthma. Reslizumab is currently available in 10ml vials containing 100mg of reslizumab. However, given that a 25mg vial size will shortly be available, the base case analysis is based on this option. The recommended dose of reslizumab, 3.0mg per kg body weight, is administered once every four weeks. Reslizumab is intended for long-term treatment and the decision to continue therapy is based on disease severity and level of exacerbation control.

Comparator 1: Add-on Omalizumab

Omalizumab as add-on therapy to BSC is a comparator for patients with severe persistent allergic asthma with elevated blood eosinophils. Omalizumab is a humanised monoclonal anti-

IgE antibody, recommended by NICE (TA278) as an option for treating severe persistent confirmed allergic IgE-mediated asthma in people who need continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year). The add-on omalizumab considered in this submission is available in a 75mg pre-filled syringe, administered every four weeks.

Comparator 2: Best standard of care (BSC) alone

BSC is defined in the CS as being based on the use of a Personal Asthma Action Plan, the avoidance of environmental/dietary triggers and the use of recommended medications (described in section 2.3). The CS states that their definition matches the BTS/SIGN guidelines. In the company model, BSC was given the same effect as the placebo arms from the pivotal trials.

The anti-IL-5 monoclonal antibody mepolizumab is licensed as an add-on treatment for severe refractory eosinophilic asthma in adults, but is not considered as a comparator in the NICE scope for this assessment.

4.3.5 Clinical effectiveness parameters

For each treatment arm, the company estimated sets of probabilities for transitions between the six health states in their model: “controlled asthma”, uncontrolled asthma”, “moderate exacerbations” and “severe exacerbations”, and the two mortality states “asthma related mortality” and “all-cause mortality”.

As noted above, for the two active treatment arms (reslizumab and omalizumab) the model included assessments for response at week 16, at week 52, and at each year thereafter, and patients categorised as non-responders at these times were assumed to stop treatment and transfer to the BSC arm. The model therefore included three sets of transition probabilities for reslizumab and for omalizumab, covering the three periods of time: 0 to 16 weeks, 16-52 weeks and post 52 weeks. Thus, the model included 7 transition matrices in total: one for BSC and three each for reslizumab and omalizumab.

The company conducted a systematic literature review and direct and indirect meta-analyses to identify and summarise evidence of the efficacy and safety of reslizumab versus BSC and versus omalizumab, as described in section 3 above. However, they used data from separate arms of studies 3082 and 3083 to estimate the transition matrices for BSC and reslizumab, rather than using comparative relative risk estimates from their meta-analysis. The company reports that transition probabilities for omalizumab were estimated using relative rates of exacerbations compared with BSC from their ITC report (see section 3.1.7.3) for 0-16 weeks, and from the omalizumab HTA [45] for post-16 weeks.

Each transition matrix was estimated using a four stage process:

1) the conditional probabilities of transitions between the three mutually exclusive states of controlled asthma, uncontrolled asthma and exacerbation (pooling together moderate and severe) were estimated;
2) the exacerbation probabilities were adjusted using a multiplier based on the observed rates of exacerbations in the year before baseline in studies 3082 and 3083, in an attempt to reflect rates of exacerbations expected in clinical practice;
3) the exacerbations were then divided into 'moderate' and 'severe' categories, based on an estimate of the percentage of exacerbations that were severe in studies 3082 and 3083; and
4) the probabilities of non-fatal transitions were adjusted for asthma-related mortality following hospitalisation (estimated by a clinical expert) due to severe exacerbations[57] and for all-cause mortality.

The sources and methods of calculation for each set of transition probabilities are described in more detail below.

4.3.5.1 BSC treatment arm

For the BSC arm, transition probabilities were computed using patient level data from the placebo arms of trials 3082 and 3083. Within these studies, the patients were classified in one of three mutually-exclusive health states at each study visit: controlled asthma, uncontrolled asthma and exacerbation (including both moderate and severe exacerbations). The sample used to estimate the transition probabilities was the subgroup of adult patients (aged 18 years or older), at steps 4 or 5 in the GINA pathway, who had experienced at least 2 exacerbations in the preceding year (n=159). The company stated that they used this subgroup as the size of the

sample (n=91) of patients experiencing ≥3 exacerbations in the previous year (the target population) was too small for estimation of transition probabilities.

The company adjusted the exacerbation probabilities estimated from the ≥2 exacerbation subgroup to reflect the rate of exacerbations observed in the year before randomisation in the subgroup of interest (≥3 exacerbations in the base case analysis). Table 68, below, shows the data from which the multipliers were calculated (CS, Table 102).

Table 68 Mean annual rates of exacerbations in placebo arms (studies 3082 and 3083)

Subpopulation	N *	Year prior to randomisation	Year after randomisation	Multiplier for transition probabilities
Adults; GINA Steps 4 and 5	**740**	**1.99**	**1.34**	**1.535**
Adults; GINA Step 4 and 5; ≥2 exacerbations in the preceding year	[redacted]	[redacted]	[redacted]	[redacted]
Adults; GINA Step 4 and 5, ≥3 exacerbations in the preceding year	[redacted]	[redacted]	[redacted]	[redacted]
Adults; GINA Step 4 and 5, ≥4 exacerbations in the preceding year	[redacted]	[redacted]	[redacted]	[redacted]

* ERG note: the numbers of patients (N) in this table do not match the numbers of patients in the placebo arms of studies 3082 and 3083 (n=476).

Table 68 shows the mean annual rates of exacerbations for the year prior to randomisation and for the year after randomisation in the placebo arms of studies 3082 and 3083. The first row shows the overall rates for all adult patients at GINA steps 4 and 5. In this group, patients randomised to placebo had a mean of 1.34 exacerbations per year during trial follow up, while in the year prior to randomisation this rate was 1.99. The company noted that the lower rate of exacerbations in the year after randomisation compared to the year before might reflect a potential placebo effect. However, we note that it could also result from a 'regression to the mean' effect: if patients experiencing a higher than usual rate of exacerbations were more likely to have been recruited to the trials.

The second, third and fourth rows of Table 68 show the annual rates of exacerbations for three subgroups of patients: those who experienced ≥2, ≥3 and ≥4 exacerbations, respectively, in the year before randomisation. In the company base case analysis, the multiplier for the

exacerbation probability (2.15) was calculated to yield a mean rate of 4.67 exacerbations per year in the BSC arm. Similarly, the multipliers for the subgroup analyses for the whole group of adults at GINA stage 4/5 (1.535), and for those with ≥2 (1.59) and ≥4 (2.62) exacerbations were calibrated to achieve annual exacerbation rates in the BSC arm of 1.99, 3.37 and 5.81 respectively.

The proportion of exacerbations that were severe (associated with systemic corticosteroid use) was estimated from the total number of exacerbations in the placebo arms of studies 3082 and 3083: 81.8% (no information is provided in the CS regarding the denominator used for this estimate).

Table 69 shows the transition probabilities for the BSC arm in the base case population of adults at GINA stage 4/5 with ≥3 exacerbations in the previous year (CS Table 103).

Table 69 Transition probabilities for the BSC arm

		Visit i +1			
		Controlled	Uncontrolled	Moderate exacerbation	Severe exacerbation
Visit i	Controlled	0.55	0.20	0.05	0.21
	Uncontrolled	0.12	0.50	0.07	0.31
	Moderate exacerbation	0.19	0.40	0.08	0.34
	Severe exacerbation	0.19	0.40	0.08	0.34

The ERG considers that the transition probabilities used in the model should be interpreted with caution. Following a request from the ERG via NICE (clarification B1), the company provided an additional file with information relevant to the transition probabilities for the reslizumab arm. However, no additional information was provided for the BSC arm. Therefore we have not been able to replicate the calculations used to generate the transition probabilities in Table 69. We also question whether the 'multiplier' approach described above to adjust exacerbation rates for a potential placebo effect and the population of interest is appropriate.

Mortality rates

In addition to the conditional transition probabilities for the non-fatal health states described above, the company model included transitions to two absorbing states: all cause and asthma-related mortality.

For all-cause mortality the transition probabilities for the all-cause mortality state were taken from the National UK life tables[58] and were adjusted for cycle length.

For asthma-related mortality the company states that transitions from severe exacerbation to asthma-related mortality could not be estimated from the clinical trials, as severe exacerbations are rare events. This transition probability was therefore calculated using odds ratios from a study by Roberts and colleagues,[57] which describes trends in 30-day case-fatality following hospitalisation for asthma in adults in Scotland from 1981 to 2009. These ratios were adjusted by the company and applied to the National UK life table to estimate the probability of asthma-related mortality. The estimated probabilities of death due to severe asthma exacerbations were only applied to exacerbations leading to hospitalisation. The proportion of severe exacerbations leading to hospitalisation were estimated by the company based on data provided by a clinical expert, who estimated the mean annual rate of exacerbations in a cohort of patients with severe asthma in England (3.06) and the mean annual number of exacerbations leading to hospitalisation (0.76). These rates were used to estimate the proportion of severe asthma exacerbations leading to hospitalisation (0.76/3.06=24.8%). The ERG questions the validity of basing this parameter on a judgment by an individual clinician.

4.3.5.2 Reslizumab arm

As for the BSC arm, the company estimated transition probabilities between three health states (controlled asthma, uncontrolled asthma and exacerbation) based on individual patient data from the reslizumab arms of studies 3082 and 3083, for adult patients, GINA steps 4/5 with 2 or more exacerbations in the previous year. The company estimated three sets of probabilities from transitions between these three health states in three time periods: 0 to 16 weeks, 16-52 weeks, and post 52 weeks.

0-16 weeks

The transition probabilities between uncontrolled asthma, controlled asthma and exacerbation were estimated for patients in the reslizumab arms of 3082 and 3083 (adults, GINA steps 4/5 and ≥3 exacerbations in the previous year) [redacted] between weeks 0 and 16.

The company states that in order to maintain the relative treatment effect of reslizumab, they applied the same multiplier as for the BSC probabilities (2.15 in the base case), to all transition probabilities of moving in to the exacerbation health state. The rationale for applying this multiplier in the reslizumab arm is unclear, since it is calculated to produce the exacerbation rate in the subgroup of interest in the placebo arm the year before randomisation – and hence adjusts for a potential 'placebo effect'.

The proportion of exacerbations that were severe (associated with systemic corticosteroid use) were estimated from studies 3082 and 3083: 76.3% in the reslizumab arms. This proportion was assumed to be the same for the three time periods in the reslizumab arm: 0-16 weeks, 16-52 weeks and >52 weeks. The company did not state the number of patients (denominator) for this percentage.

Table 70 presents the company base case conditional transition probabilities for the non-fatal health states over 0 to 16 weeks (CS Table 106). The same mortality rates were used as in the BSC arm.

Table 70 Transition probabilities 0-16 weeks: reslizumab arm

		Visit i +1			
		Controlled	Uncontrolled	Moderate exacerbation	Severe exacerbation
Visit i	Controlled	0.72	0.25	0.01	0.03
	Uncontrolled	0.27	0.54	0.04	0.14
	Moderate exacerbation	0.16	0.48	0.08	0.27
	Severe exacerbation	0.16	0.48	0.08	0.27

Following a clarification request from the ERG via NICE (clarification B1), the company provided a confidential Excel file containing data that they used to calculate the transition probabilities from the reslizumab arms of 3082 and 3083. The proportions of transitions between

consecutive, 4-weekly visits between baseline and week 16 are presented in Table 71. ~~However, t~~The transition probabilities in Table 70 differ from those in Table 71 *because of the use of the multiplier to adjust the rate of exacerbations to match that in the year before baseline for patients with 3 or more exacerbations in that year* ~~, and we could not replicate how company calculated the transition probabilities used in the model~~.

Table 71 Transition probabilities (0-16 weeks) directly obtained from the number of transitions at consecutive monthly assessments in studies 3082 and 3083

		Visit i +1		
		Controlled	Uncontrolled	Exacerbation
Total reslizumab population	Controlled	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]
	Exacerbation	[redacted]	[redacted]	[redacted]

16 - 52 weeks

The model introduces a response rule at 16 weeks. Response rates at week 16 were estimated from studies 3082 and 3083: see Table 72 (CS Table 105). In the model, patients classified as 'responders' or 'indeterminate' were assumed to continue reslizumab treatment, while those classified as 'non-responders' transferred to the BSC treatment arm and used that arm's transition probabilities and costs for the remainder of the time horizon. In the company base case, 13.2% of patients were assumed to stop treatment at week 16. We note that the company has not specified the denominator for the percentages in Table 72.

Table 72 Response rates of the reslizumab-treated population,

	Responders	Non-responders	Indeterminate	Total
Adult patients at GINA Step 4/5: ≥2 exacerbations in the preceding year	78.3%	13.2%	8.5%	**100%**
Adult patients at GINA Step 4/5	81%	10%	9%	**100%**

Transition probabilities from week 16 to week 52 were estimated using data on observed transitions from the reslizumab arms in studies 3082 and 3083 (excluding the non-responders at 16 weeks). The same multiplier as in the BSC treatment arm (2.15 for the base case) was applied to the exacerbation probabilities, and the same percentage of exacerbations (76.3%)

were assumed to be 'severe'. Table 73 shows the 16-52 week reslizumab transition probabilities used in the CS model base case (CS Table 107).

Table 73 Transition probabilities 16-52 weeks: reslizumab arm

		Visit i +1			
		Controlled	Uncontrolled	Moderate exacerbation	Severe exacerbation
Visit i	Controlled	0.81	0.15	0.01	0.03
	Uncontrolled	0.23	0.70	0.02	0.06
	Moderate exacerbation	0.42	0.45	0.03	0.11
	Severe exacerbation	0.42	0.45	0.03	0.11

Table 74 shows the directly obtained transition probabilities reported in the company's response to clarification question B1 for the non-responder [redacted] and indeterminate response [redacted] population: based on [redacted] transitions observed between consecutive, 4-weekly assessments from 16-52 weeks after randomisation. As for the transition probabilities for 0 to 16 weeks, ~~it is not clear why~~ these differ from the set of probabilities used in the model *because of the use of the multiplier to adjust the rate of exacerbations to reflect that in the year before baseline for the subgroup with three or more exacerbations in that year* (Table 73).

Table 74 Transition probabilities (16-52 weeks) directly obtained from the number of transitions (visits)

		Visit i +1		
		Controlled	Uncontrolled	Exacerbation
Total reslizumab population	Controlled	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]
	Exacerbation	[redacted]	[redacted]	[redacted]

After 52 weeks

A second assessment of response is made after 52 weeks of treatment with reslizumab. The company states that patients whose asthma remained uncontrolled or who experienced moderate or severe exacerbations for 12 consecutive months (13 consecutive cycles) were assumed to discontinue treatment and transfer to the BSC arm. Thus, to be classed as 'responders' and to continue treatment after 52 weeks, modelled patients had to be in the

'controlled' health state at one or more cycle during the first year. The same rule was then applied at each successive anniversary, and any patients who remained in the uncontrolled or exacerbation health states for the whole year were assumed to discontinue treatment (described in section 4.3.2).

No data were available for treatment beyond 52 weeks. The transition probabilities beyond 52 weeks were therefore estimated based on transitions during the period 16-52 weeks for patients in the reslizumab arms of studies 3082 and 3083 who were identified as 'responders' at 16 weeks [redacted] (CS page190) – note that patients classified as 'indeterminate response' at 16 weeks were not assumed to continue treatment after 52 weeks. The same multiplicative factor (2.15) and proportion of exacerbations that were 'severe' (76.3%) were applied as in the 0-16 week and 16-52 week periods for reslizumab. Table 75 presents the transition probabilities used in the model for the reslizumab arm post-52 weeks (CS Table 108).

Table 75 Transition probabilities post-52 weeks: reslizumab arm

		Visit i +1			
		Controlled	Uncontrolled	Moderate exacerbation	Severe exacerbation
Visit i	Controlled	0.82	0.14	0.01	0.03
	Uncontrolled	0.25	0.71	0.01	0.03
	Moderate exacerbation	0.59	0.41	0	0
	Severe exacerbation	0.59	0.41	0	0

Table 76 presents the set of probabilities estimated using the transitions of patients classified as 'responders' [redacted] at the 16-week assessment. These probabilities differ slightly from those in Table 74, because the former includes patients assessed as having an 'indeterminate' response at 16 weeks in addition to those classed as 'responders'.

Table 76 Transition probabilities (post-52 weeks) directly obtained from the number of transitions (visits)

		[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

As with the 0-16 week and 16-52 week data, ~~we have concerns regarding the calculation of the post 52 week transition probabilities for reslizumab. T~~the transition probabilities used in the model (Table 75) *were adjusted to reflect the rate of exacerbations in the year before baseline for the subgroup with 3 or more exacerbations in that year* ~~are not identical to the probabilities reported from the individual patient data (Table 76) and the ERG could not check the validity of the company estimates or replicate their calculations~~.

4.3.5.3 Omalizumab arm

Due to limited data availability, the company states that it was not possible to conduct a comparison in the overlap population eligible for both omalizumab and reslizumab (i.e. patients with both an eosinophilic [IL-5-mediated] and allergic [IgE-mediated] asthma phenotype). The company instead reports that the relative treatment effect for omalizumab versus BSC was estimated from the total population enrolled in the omalizumab clinical trials, which included patients with lower levels of blood eosinophils. The underlying assumption was that the relative treatment effect of omalizumab was similar in patients with both normal and elevated levels of eosinophils.

As for reslizumab, transition probabilities for omalizumab were estimated for three time periods, based on assessments for response at 16 and 52 weeks:

- Transition probabilities from 0 to 16 weeks;
- Transition probabilities from 16 to 52 weeks for patients assessed as responding or with indeterminate response to treatment at week 16; and
- Transition probabilities after 52 weeks for patients assessed as responding at 52 weeks.

0 – 16 weeks

The company states that the impact of omalizumab on the number of exacerbations was estimated using the relative rate of exacerbations compared with BSC at 52 weeks, which the CS states was obtained from the ITC, cited as 0.82 (CS p191). However, we have not been able

to identify the source of this relative rate. As described in section 3.1.7.3, a direct comparison of clinically significant exacerbation rates in the omalizumab trials is not provided in the ITC Report.

The company assumed that the proportion of exacerbations that were classed as severe with omalizumab was the same as with reslizumab (76.3%).

Due to a lack of data, the company assumed that the conditional probabilities of moving between the controlled asthma and uncontrolled asthma health states, in patients not experiencing an exacerbation, were the same with omalizumab as with reslizumab. The company noted that this was likely to be a conservative assumption, as the ITC Report based on double blind trials estimated mean ACQ results at 16 weeks as more favourable for reslizumab than for omalizumab. However, as noted above, the ERG has serious concerns about the reliability of the ITC results.

Table 77 below shows the company base case transition probabilities for 0 to 16 weeks for the omalizumab arm, based on the subgroup with 3 or more exacerbations in the preceding 12 months (CS Table 109).

Table 77 Transition probabilities for the omalizumab arm 0-16 weeks

		Visit i +1			
		Controlled	Uncontrolled	Moderate exacerbation	Severe exacerbation
Visit i	Controlled	0.59	0.20	0.05	0.16
	Uncontrolled	0.23	0.46	0.07	0.24
	Moderate exacerbation	0.17	0.50	0.08	0.26
	Severe exacerbation	0.17	0.50	0.08	0.26

16 – 52 weeks

The estimated transition probabilities for omalizumab between 16-52 weeks (CS Table 110) are shown in Table 78. The company cited the percentage of patients assessed as responding to omalizumab at 16 weeks as 56.5%, and the relative rate of exacerbations in responders to omalizumab compared with patients on BSC as 0.373; both taken from the INNOVATE trial[34]

and the omalizumab HTA.[47] We note that there is a difference between the relative risk of exacerbations used for the pre- and post-16 week transition probabilities (0.82 and 0.373 respectively). This difference might be attributable to the fact that the pre-16 week relative risk refers to the whole group of patients, while the post-16 week relative risk refers to responders. However, we were unable to locate these rates in the referenced sources.

As in the 0-16 week time period, the company assumed that the transition probabilities between controlled and uncontrolled asthma, and the proportion of exacerbations that were severe, were the same for omalizumab as for reslizumab.

Table 78 Transition probabilities for the omalizumab arm (16 to 52 weeks)

		Visit i +1			
		Controlled	Uncontrolled	Moderate exacerbation	Severe exacerbation
Visit i	Controlled	0.61	0.11	0.07	0.21
	Uncontrolled	0.19	0.58	0.06	0.18
	Moderate exacerbation	0.38	0.40	0.05	0.17
	Severe exacerbation	0.38	0.40	0.05	0.17

Post 52 weeks

As with reslizumab, the company assumed that patients on omalizumab would be assessed for response every year, and that patients who remained in the uncontrolled or exacerbation health states for the whole year would discontinue treatment and transfer to the BSC arm. This assumption was validated by a panel of UK clinical experts. The percentage of patients classified as responders, who therefore remained on treatment, was assumed to be the same for all time periods.

As for the 16-52 week period, the relative risk of exacerbation after 52 weeks with omalizumab versus BSC in responders was estimated at 0.373 (cited as coming from the INNOVATE trial[34] and the omalizumab HTA.[47]) The percentage of exacerbations that were classed as severe post 52 weeks is not explicitly reported in the CS, but we assume this is the same as for the 0 to 16 week period (76.3%). And, again, as for 0-16 weeks, the omalizumab transition probabilities

between controlled and uncontrolled asthma health states were based on the reslizumab transition probabilities due to lack of data(CS Table 111). Table 79 shows the transition probabilities for omalizumab post 52 weeks.

Table 79 Transition probabilities for the omalizumab arm (post-52 weeks)

		Visit i +1			
		Controlled	Uncontrolled	Moderate exacerbation	Severe exacerbation
Visit i	Controlled	0.77	0.13	0.02	0.07
	Uncontrolled	0.22	0.64	0.03	0.11
	Moderate exacerbation	0.50	0.35	0.04	0.12
	Severe exacerbation	0.50	0.35	0.04	0.12

4.3.5.4 ERG view on clinical effectiveness parameters

Overall, the ERG has concerns regarding the estimates of clinical effectiveness parameters used in the company model:

Firstly, we question the use of a multiplier to adjust the exacerbation probabilities in the BSC and reslizumab arms. The CS implies that this multiplier has two purposes:

- The multiplier is used to adjust the baseline risk of exacerbation for different subgroups (all adults at GINA step 4/5, and those with ≥2, ≥3 and ≥4 exacerbations in the preceding year). We consider that adjusting for different baseline levels of risk in subgroup analysis is appropriate. However, we suggest that the base case analysis should reflect the observed levels of risk in the trial populations.

- The second reason that the company gives for use of the multiplier is to correct for a potential placebo effect by calibrating the model to produce the observed rate of exacerbations with BSC in the year before randomisation (Table 68). If the observed fall in exacerbation rates from the year before to the year after randomisation was attributable to a placebo effect, it would be unconventional but not unreasonable to correct for it, as patients receiving BSC in routine clinical practice would not be given a placebo, and so would not gain this psychological benefit. However, it is not clear why

the adjustment for a potential placebo effect should also be applied to the reslizumab arm, since in clinical practice these patients would know that they were receiving treatment, and hence might gain a psychological benefit from treatment in addition to the direct effects of the active treatment.

- The company argue that the multiplier has to be applied to the exacerbation rates in the reslizumab arm to retain the relative treatment effects estimated from the clinical trials. However, it would be more appropriate to do this directly by modelling the BSC arm using an absolute risk estimate, and to adjust this for the reslizumab arm by multiplying by the relative risk. This would retain randomisation, and provide more a meaningful reflection of uncertainties over the absolute and relative risks in the probabilistic sensitivity analysis. The company have used this more conventional approach for the omalizumab arm of their model.

- Furthermore, it is not clear that the lower rate of exacerbations in the year after randomisation compared with the year before is attributable to a placebo effect. It also might result (at least partly) from a 'regression to the mean' effect. This would occur if patients were more likely to be recruited into the trials at times when they were experiencing, due to chance, higher rates of exacerbations than they would usually. If so, one would expect exacerbation rates to fall naturally over time, as patients revert to a more typical pattern of disease. It is therefore unclear whether there is a need to adjust the trial results to the observed exacerbation rates in the year before study entry.

We also have concerns over the lack of clarity over the calculations used to estimate the transition probabilities. In response to a clarification question, the company did supply data underlying the transition calculations for the reslizumab arm, ~~but we could not replicate the probabilities used in the model from these data, and~~ but no data were provided to justify the calculations for the BSC arm.

The company's estimates of transition probabilities for the BSC arm were based on patients experiencing ≥2 exacerbations, instead of their target population for the base case model of ≥3 exacerbations. This was justified due to the small sample size (n=91) in the latter group. However, we note that the company based their estimates of transition probabilities for the reslizumab arm on similar samples of just over 100 patients. Direct estimation of transitions for

the populations of interest, with uncertainty reflected in the PSA, would have been more appropriate.

The company's assessment of response at 16 weeks was based on an algorithm used to predict the result of the 52-week assessment. However, no information was provided regarding the coefficients of the prediction model, measures of model fit, or it's predictive validity in an external dataset.

For the transition probabilities used in the omalizumab arm, we were not able to check the relative risks of exacerbation used in the model: 0.82 for patients treated before the response assessment at 16 weeks, due to lack of clarity of the source cited in the CS.

Another concern over the clinical effectiveness parameters arises from the lack of evidence relating to the effectiveness of reslizumab beyond 52 weeks, and the underlying assumption that effects observed up to 52 weeks will persist up to 60 years duration. This is a strong assumption.

4.3.6 HRQoL

4.3.6.1 Systematic review of HRQoL studies

A systematic review was conducted by the company to identify HRQoL values. We report the details of that systematic review in Section 4.2 with inclusion and exclusion criteria given in Table 65. CS Section 5.4.3 provides details of the 13 HRQoL studies identified through the systematic review of HRQoL. However, the primary study used for HRQoL was Willson and colleagues,[44] a study that was identified through the cost-effectiveness review and not identified in the HRQoL review. Willson and colleagues contains directly measured EuroQoL-5 dimensions (EQ-5D) data from people with severe asthma, that it was missed is a shortcoming of the HRQoL search. The one other study that was used for utility values, Lloyd and colleagues,[59] was identified through the systematic review of HRQoL studies and is also referenced in Willson and colleagues. No justification was provided for the choice of HRQoL studies used in the model.

The systematic review of HRQoL studies did not report any quality assessment. Willson and colleagues was quality assessed for the systematic review of cost-effectiveness studies (CS Appendix 7).

ERG searches for additional HRQoL data

The ERG ran some searches to identify quality of life data that may have been missed due to the exclusion criteria on the company systematic review. These searches consisted of the searches for studies in the NHS EED and HTA databases (see Section 4.2), as well as searches using the Ovid platform (MEDLINE, Embase, MEDLINE in process). The searches on the Ovid platform contained the following search terms: severe asthma, QALY*, EuroQoL*, EQ-5D*, AQLQ, and SGRQ—asterisks represent wildcards that can take any value after the preceding term. No date limitations were applied. None of the studies identified by the ERG were included in the company's systematic review of HRQoL. These searches identified the four cost-utility analyses identified in Section 4.2: Brown and colleagues,[51] Dewilde and colleagues,[52] Gerzeli and colleagues,[53] and Morishima and colleagues;[54] and one study by Szende and colleagues[60] that was referenced in Morishima and colleagues.[54] The next several paragraphs identify the methods used to measure utility in the five studies identified through the ERG's additional searches.

Brown and colleagues and Dewilde and colleagues[51, 52] used treatment-based utilities derived from mapped instruments in trials and exacerbation utilities from Lloyd and colleagues.[59]

Gerzeli and colleagues used utility scores for health states for successful control, sub-optimal control, outpatient managed exacerbation and inpatient managed exacerbation.[53] These health states are very comparable to those used in the CS. The utility scores for these health states were synthesized from five cited studies[61-65] All these studies,except Edelen and colleagues[63] used EQ-5D. The health state values in Gerzeli and colleagues were as follows: Successful control: 0.85; Suboptimal control: 0.77; Outpatient managed exacerbation: 0.66; Inpatient managed exacerbation: 0.59.

Morishima and colleagues[54] used utility scores derived from a study by Szende and colleagues[60] which used three questionnaires (EQ-5D, SF-36, and SGRQ; and a direct time trade-off exercise) to measure HRQoL in patients with varying levels of asthma control. The

levels of control were good control, mildly reduced control, moderately reduced control, and poor control. These utility values were as follows: good control: 0.93; mildly reduced control: 0.76; moderately reduced control: 0.65; poor control: 0.52. Morishima and colleagues used poor control to represent moderate and severe exacerbations in their cost-utility model.

In general, studies had higher utility values for patients in exacerbation states than the company's model. The searches conducted by the ERG were not meant to be comprehensive or conclusive, but demonstrate that there were other potential utility scores that could have been used to represent health states in the company model.

4.3.6.2 HRQoL values used in the company model

HRQoL data enter the company model as utility values attached to health states. The health states are related to asthma control and exacerbation status; these health states appear consistent with disease processes and patient experience. Briefly, utility values were assigned to four health states: controlled asthma, uncontrolled asthma, moderate exacerbation, and severe exacerbation. Section 4.3.2 describes these health states in further detail. The utility scores used in the model (CS Table 115) are reported in Table 80. The economic model does not include the effects on HRQoL due to adverse events. Adverse events were not modelled, as the pivotal reslizumab trials found adverse events between reslizumab and placebo to be comparable and not statistically significantly different.[19] We find this justification reasonable.

Table 80 Summary of utility values for the company cost-effectiveness model (CS Table 115, p. 201)

Health state	Utility value	95% CI	Reference in submission	Justification
Uncontrolled asthma	0.728	0.707; 0.749	Willson et al, 2014[44]	Health state definition used in the model is reconcilable with the definition used in this study.
Controlled asthma	0.920	0.901; 0.943		
Moderate exacerbation	0.57	0.549; 0.591	Lloyd et al, 2007 Willson et al, 2014 [44, 59]	
Severe exacerbation	0.33	0.309; 0.351		

Willson and colleagues[44] used an economic model to assess the cost-effectiveness of tiotropium bromide in patients with uncontrolled asthma on ICS/LABA therapy. Utility data in Willson and colleagues and the company's model for the uncontrolled asthma and controlled asthma health states were derived from the PrimoTinAsthma trials. These trials were 48 weeks

long, with 912 patients at GINA steps 4 and 5. The trial population appears similar to reslizumab's treatment indication and appears appropriate. Utility scores were derived from EQ-5D data collected in patients and valued using the United Kingdom tariff. The methods used to derive utility scores in Willson and colleagues are appropriate, and consistent with preferred methods in the NICE Reference Case.[12]

Lloyd and colleagues[59] was a four-week observational study that measured the HRQoL impacts of exacerbations in 112 patients with BTS level 4 and 5 asthma. EQ-5D questionnaires were used to collect HRQoL data from patients, and valued using the UK tariff. The utility scores in the model were for moderate exacerbations (22 patients), defined as exacerbations that did not require hospitalisation but required oral steroids; and severe exacerbations (5 patients), defined as exacerbations that required hospitalisation. HRQoL data were collected at baseline (when no patients were experiencing exacerbations) and at four weeks. HRQoL data were not measured during exacerbations, so it is unclear how much effect recall bias may have on the results. Lloyd and colleagues did not report the length of time that patients experienced exacerbations, but did report the time period between assessments (4 weeks). In the related NICE STA of mepolizumab this time between assessments was used to assume the duration of exacerbations, but was criticised by the Appraisal Committee.[48] Similar to the mepolizumab model, the reslizumab CS applies the decreased utility across four weeks.[48] When calculating health state costs, the CS assumes that a cycle in the moderate exacerbation health state consists of one week of moderate exacerbation costs and three weeks of uncontrolled asthma costs. Severe asthma consists of two weeks of exacerbation costs and two weeks of uncontrolled asthma. It is unclear why the assumptions on HRQoL are different from the assumptions on resource use. In the NICE MTA of omalizumab TA278,[47] the mean length of exacerbations was two weeks. For further detail on health state cost calculation, see Section 4.3.7.2.

The specific utility values used in the company's model are all reported in Willson and colleagues (Table 2, p. 451, in Willson and colleagues).[44] The utility scores for controlled and uncontrolled asthma were derived from Willson and colleagues whilst the utility scores for moderate and severe exacerbations were derived from Lloyd and colleagues.[44, 59] We checked that the utility scores reported in the CS agree with those reported in Wilson and colleagues and Lloyd and colleagues. There appears to be a minor error in the reporting of the utility score for controlled asthma. The CS states that the 'Controlled asthma' health state utility was estimated

as a weighted average of the controlled and partly controlled health state utilities from Willson and colleagues.[44]

The weighting was derived from the pivotal reslizumab trials (3082 and 3083). Controlled asthma was defined as having an ACQ <1.5, which includes patients with partially controlled asthma (ACQ between 1 and 1.5) and controlled asthma (ACQ <1). Experts we consulted indicated that the controlled threshold should be an ACQ of 0.75. This would indicate that quality of life may be overestimated in the controlled health state of the model.

In the pivotal clinical trials 49% of the assessments with an ACQ<1.5 had scores between 1 and 1.5. When we calculated the utility score using these weightings, we obtained 0.9223, whilst the CS reports a utility score of 0.920 for the controlled asthma health state. The confidence intervals reported in the CS for the weighted average are correct. We have tested the effects of the corrected point estimate, and it does not make a meaningful difference to the results. Additionally, the value used in the probabilistic sensitivity analysis in the model is different from those listed above. The mean controlled utility value in the probabilistic model is 0.937, which corresponds to the value for fully controlled asthma in Willson and colleagues.[44]

4.3.6.3 Methodological discrepancies across studies in exacerbation definitions and utility score calculation

There are some differences in the definitions of exacerbations between Lloyd and colleagues,[59] Willson and colleagues,[44] and the CS. Lloyd and colleagues and Willson and colleagues define severe exacerbations as requiring hospitalisation. In the CS, only 24.84% of patients with a severe exacerbation are hospitalised. This indicates that the severity of exacerbation in the CS is overestimated. We conducted a sensitivity analysis (section 4.4) using a weighted average of utility scores for the severe exacerbation state. In our analysis, 24.84% of the utility score is derived from the utility score for severe exacerbations (0.33) whilst the remaining weight is derived from the utility score for moderate exacerbations (0.57), resulting in an overall utility score of 0.510 for severe exacerbations.

The utility sources chosen appear to be appropriate, but it should be noted that the exacerbation data for moderate exacerbations in Lloyd and colleagues are based on 22 patients and the severe exacerbation data are based on 5 patients. These data are derived from EQ-5D and are

appropriate, but data from the pivotal trials from patients with exacerbations may be more robust due to the larger sample size of patients with exacerbations (224 patients according to CS Table 20), but these data would be need to be mapped from AQLQ. A sensitivity analysis was conducted by the company that used mapped utility scores from AQLQ but only included mapped utilities for the controlled and uncontrolled asthma health states. The ERG suggests it would have been more appropriate to explore all utility values using data from the pivotal reslizumab trials. The NICE Decision Support Unit recommends in Technical Support Document 12 that wherever possible utility scores should all be derived from the same study for the CS;[66] this would only be possible by mapping from AQLQ from the pivotal reslizumab trials. Whilst the ERG requested full details of the AQLQ and mapped EQ-5D utilities, none were provided by the company. The pivotal trials did not utilize EQ-5D. We note that the Appraisal Committee for the NICE STA of mepolizumab was critical of the use of mapped utilities from St. George's Respiratory Questionnaire (SGRQ) and indicated that they preferred the EQ-5D utility scores measured directly from the trial where the mapped algorithm for SGRQ were derived.[48] However, the lack of robustness in the exacerbation utility values in Lloyd and colleagues makes using other data a legitimate and potentially preferable methodological option.

In addition to HRQoL data used in the model, the company's systematic review of economic evaluations identified studies that provided HRQoL: Norman and colleagues, and two studies by Faria and colleagues (derived from TA278).[47]

There were several differences in utility measurement methods between the model in Norman and colleagues and the CS model.[47] In Norman and colleagues the primary source of utility data for patients with severe asthma in the omalizumab technology appraisal was data from the EXALT trial taken from the Novartis CS, but this trial was not identified through systematic searches and the data extractions for economic evaluations and quality of life studies do not report original sources[47] The EXALT trial measured utility by treatment status, not by asthma control. Utility data from Lloyd and colleagues was used in Norman and colleagues, and is also used in the CS model to define utility for exacerbation health states.[59]

However, Norman and colleagues used disutilities that are applied to treatment states to incorporate the effect of exacerbations on HRQoL, whilst the CS uses the absolute value reported in Lloyd and colleagues.[59] These disutilities are calculated from Lloyd and colleagues using a difference from baseline approach, whilst the CS (and Willson and colleagues) use

absolute utility values. A change from baseline approach results in a smaller decrease in HRQoL due to exacerbation and also better reflects the severity of the population. Table 81 provides the utility values from Lloyd and colleagues.

The ERG used the reported data for the change from baseline to calculate the baseline utility values for each state in Lloyd and colleagues. Patients who had a moderate exacerbation during the four week observational study had a baseline utility of 0.67 and patients who had a severe exacerbation had a baseline utility of 0.53. Both of these are substantially lower than the uncontrolled asthma utility score from Willson and colleagues of 0.728.[44]

Table 81 Health utilities reported in Lloyd and colleagues[59]

Health State	Extrapolated EQ-5D at baseline	EQ-5D Utility Score at 4 week follow-up	EQ-5D change from baseline score, additive (4 weeks)	EQ-5D change from baseline, multiplicative ratio (4 weeks)
No exacerbation[a]	0.87	0.89	0.02	1.02
Exacerbation with oral steroids[b]	0.67	0.57	-0.10	0.85
Hospitalised[c]	0.53	0.33	-0.20	0.62
[a] Utility score not used in the company model; [b] utility value used for moderate exacerbation in CS; [c] utlity value used for severe exacerbaation in CS				

The NICE Decision Support Unit (DSU) provides advice on using utility scores to represent health states in modelling in Technical Support Document (TSD) 12.[66] We have conducted scenario analyses to address these methodological discrepancies using the additive model and multiplicative methods for combining utility scores from multiple health states (section 4.4).

4.3.6.4 Comparison to other technology appraisals

The economic model does not include discontinuation of oral corticosteroids, as the pivotal trials did not allow discontinuation.[19] Clinical experts informed us that discontinuing oral corticosteroids would be expected to coincide with reductions in long-term risks and symptoms and that it was plausible that patients on reslizumab may reduce or discontinue oral corticosteroid use. Additionally, Norman and colleagues[47] conducted an analysis where patients were allowed to discontinue oral corticosteroids. This analysis lowered the risk and associated HRQoL loss associated with type 2 diabetes, myocardial infarction, osteoporotic fracture,

glaucoma, ulcer, cataracts and stroke. The model may underestimate some benefits for both reslizumab and omalizumab by not allowing patients to discontinue oral corticosteroids. The effect of reducing oral steroid use was considered in the NICE STA of mepolizumab.[67] The Appraisal Committee concluded that there could be significant benefits to patients and carers from reduction of oral corticosteroid use.[67]

One of the clinical comparators for reslizumab is mepolizumab, although it is not included in the NICE scope for the current technology appraisal. Utility scores in the NICE STA of mepolizumab were mapped from SGRQ values to EQ-5D, and exacerbation disutilities were derived from Lloyd and colleagues and applied using the absolute change from baseline values.[48] The utility scores used in the NICE STA of mepolizumab (Table 55 in the mepolizumab ERG report) are shown in Table 82.

The NICE Appraisal Committee was critical of the use of mapped utilities in the NICE STA of mepolizumab.[67] In the company's model for reslizumab, unlike in the mepolizumab STA, there were no EQ-5D scores directly available from the pivotal trials, and the exacerbation disutilities used in Norman and colleagues and the NICE STA of mepolizumab are from poor quality data.[47, 48] The ERG considers that mapped utilities may have provided more robust estimates for utility scores, and for the disutility associated with exacerbations. NICE Technical Support Document 12 also supports deriving utility scores from one source if at all possible to give the most internally consistent measurements.[66]

Table 82 Utility scores used in the NICE STA of mepolizumab

	ITT population		**Glaxo Smith Kline Per Protocol, excluding stable maintenance OCS**		**GSK Per Protocol**	
	EQ-5D	**SGRQ-mapped**	**EQ-5D**	**SGRQ-mapped**	**EQ-5D**	**SGRQ-mapped**
Mepolizumab: before CA	0.802	0.796	0.829	0.793	0.827	0.777
SoC treatment†	0.794	0.738	0.797	0.682	0.785	0.708
Mepolizumab: after CA	0.824	0.806	0.834	0.805	0.837	0.795
CA = continuation assessment †Regardless of whether patients had prior mepolizumab						

The utility scores from the NICE MTA of omalizumab and the NICE STA of mepolizumab are not directly comparable to the utility scores from the reslizumab CS as patients' utility is associated with their treatment status rather than their asthma control status.[47,48] The utility scores from these appraisals are lower than the controlled asthma utility score in the CS. However, because the health states in the omalizumab and mepolizumab models are based on treatment, they include patients with controlled and uncontrolled asthma in a single state.

4.3.6.5 Summary of health related quality of life

The utility values used in the model appear to have been broadly derived from appropriate sources, although the data on exacerbations should be viewed with caution due to the very small sample of relevant patients in Lloyd and colleagues.[59] There appear to be some small errors in the calculation of controlled asthma patient utility, but these made little difference to model results. The searches conducted for HRQoL data do not appear to have been comprehensive or sensitive enough. The primary HRQoL study was not derived from the systematic review of quality of life studies, but rather from the systematic review of economic evaluations.

We conducted searches that identified further HRQoL studies that used EQ-5D. All of the studies identified had higher utility scores than the company model for states comparable to severe exacerbations. The methods used for incorporating exacerbation utility are not consistent with previous NICE appraisals in severe asthma and are inconsistent with recommended methods from the NICE DSU.[66] All alternative methods for calculating utility scores for exacerbations result in less impact to HRQoL from exacerbations and, because of this, we find it likely that the disutility of exacerbations is overestimated in the CS.

4.3.7 Resource use and costs

The CS model contains resource use and cost data for the following categories: drugs (including administration), nurse and general practitioner visits, specialist visits, emergency medicine, and hospitalisation. Adverse events were not modelled, as the pivotal reslizumab trials found

adverse events between reslizumab and placebo to be comparable and not statistically significantly different.[19]

4.3.7.1 Drug acquisition and administration costs

Reslizumab administration is based on body weight. Reslizumab is administered at a dose of 3 mg/kg every four weeks. Drug dosage was calculated using the weight distribution in the pivotal reslizumab trials (see Figure 8).[19] The mean weight in the pivotal reslizumab trials was 75.2 kg. The base case model assumes no vial sharing. The company conducted a scenario analysis assuming vial sharing. The manufacturer did not consider drug wastage relevant to any comparators.

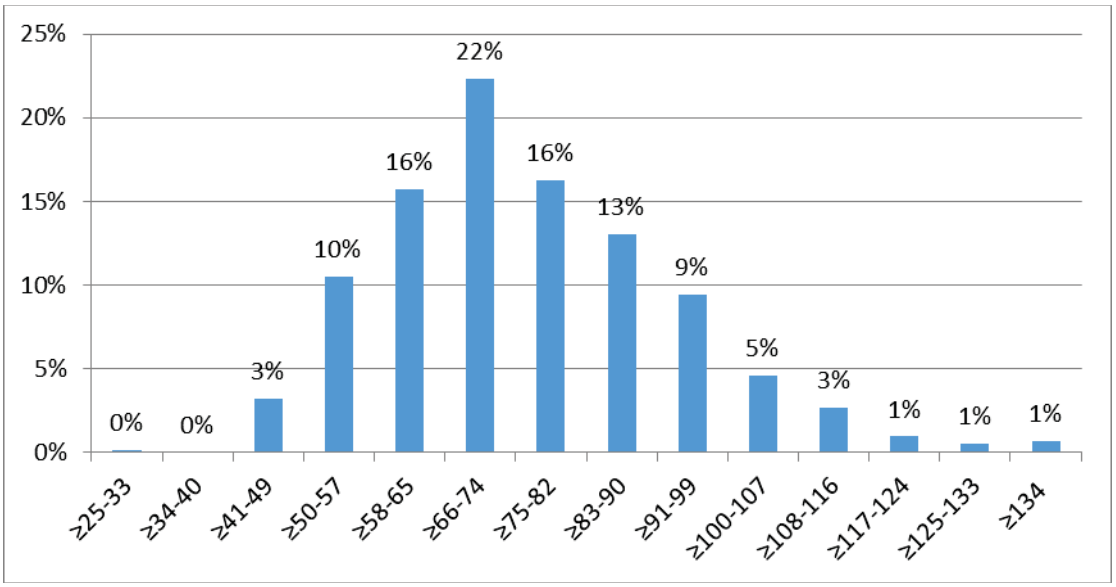


Figure 8 Weight distribution in kg – adult patients at GINA Step 4/5 enrolled in trials 3082 and 3083

Reslizumab is currently only available in 10mL vials that contain 100mg of reslizumab. The company indicated that 25mg vials would become available between the [redacted], so they have assumed availability of these vial sizes in the model. A sensitivity analysis with 100mg vials only, and sensitivity analysis with and without vial sharing were undertaken by the company. The list price of resilizumab is £124.99 for a 25 mg vial and £499.99 for 100 mg vial. The company has provided a PAS for resilizumab (awaiting approval from the Department of Health at time of preparing this report). The analyses reported in the CS and in this report use the PAS price for resilizumab.

The administration cost of reslizumab was derived from the SmPC with input from clinical experts.[13] The company assumed that administering reslizumab required 55 minutes of specialist nurse time: 10 minutes for treatment preparation, 30 minutes for treatment administration, and 15 minutes to monitor the patient after treatment administration. One clinical expert consulted by the ERG indicated that the length of monitoring would initially be a day case admission with a tapering of monitoring time as responsiveness and safety were established for the patient. Two experts indicated that 10 minutes for treatment preparation was likely too short.

Omalizumab is administered as a subcutaneous injection every 2-4 weeks. Dosage is determined by serum total IgE levels measured before initiating treatment and body weight. The company used data from the INNOVATE trial to estimate the average dose and the number of omalizumab treatments that occur in 28 days.[34] The company submission reports the cost per cycle rather than the cost per administration of omalizumab. The analyses reported in the CS use the list price for omalizumab. Results with the confidential PAS for omalizumab are reported by the ERG in a separate confidential appendix.

Omalizumab was assumed to require 40 minutes of specialist nurse time per administration: 10 minutes to prepare and administer the treatment, and 30 minutes to monitor the patient after administration. The sources of the administration assumptions for omalizumab are not reported in the CS. The administration costs used in the CS for omalizumab differ from those used in the NICE MTA of omalizumab and the NICE STA of mepolizumab.[47, 48] In both of these sources, the monitoring time for omalizumab was estimated to require 15 minutes of specialist nurse time. Table 83 shows the effect of these differences on administration costs. We have conducted a sensitivity analysis using these alternate values (see section 4.4).

Table 83 Omalizumab administration cost differences between the CS and other NICE technology appraisals

NICE TA	Administration time (minutes)	Monitoring time (minutes)	Who administers	Total administration and monitoring costs[1]	Cycle costs
Reslizumab STA	10	30	Specialist Nurse	£39.33	£51.52
Mepolizumab STA and omalizumab MTA	10	15	Specialist Nurse	£24.58	£32.20

[1]Assuming PSSRU 2015 hourly costs for a specialist nurse at £59/hour

Table 84 reports the costs for drug administration for reslizumab and all comparators (CS Table 118). A description of the methods of calculating the drug and administration costs of best standard of care is not reported in the CS.

Table 84 Unit costs associated with the technology in the economic model

Treatment arm	Item	Cost	Source
Reslizumab (including anticipated PAS discount)	Technology cost: 100 mg/10 mL Technology cost: 25 mg/2.5 mL	[redacted]	Teva UK Limited, PAS price
	Mean cost of treatment/cycle • Base case: 25 mg vials available; no vial sharing • Scenario analysis: only 100 mg vials available; no vial sharing • Scenario analysis: vial sharing	[redacted]	Teva UK Limited, PAS price
	Administration and monitoring cost/cycle (55 minutes specialist nurse)	£54.08	PSSRU, 2015[68]
	Total	**Base case cycle cost:** [redacted]	
Omalizumab (list price)	Technology cost: 75 mg/mL	£128.07	BNF legacy, 18 March 2016[69]
	Mean cost of treatment/cycle: vial sharing	£619.60	BNF legacy, 18 March 2016[69]
	Administration and monitoring cost/cycle (40 minutes)	£39.33 1.31 per cycle £51.64/cycle	PSSRU, 2015[68] INNOVATE[34] Omalizumab SmPC[55]
	Total	**Cycle cost: £671.24 (list price)**	
BSC (fluticasone propionate + salmeterol)	Technology cost	£40.92	BNF legacy, 18 March 2016[69] Reslizumab studies 3082 and 3083[19]
	Initiation cost	0	
	Mean cost of treatment/cycle	£40.92	
	Administration and monitoring cost/cycle	0	
	Total	**£40.92**	

BNF: British National Formulary; BSC: best standard of care; CSR: clinical study report; PSSRU: Personal Social Services Research Unit.

In their response to a clarification request from the ERG via NICE, the company stated that the cycle cost of omalizumab had been underestimated (clarification Appendix 4). The corrected value for the mean cost per treatment cycle of £619.60 differs slightly from the 28 day cost

calculated from the NICE MTA of omalizumab (£617.57), but the difference is inconsequential. All ERG analyses use the revised value of omalizumab.

4.3.7.2 Health state costs

A systematic literature review was conducted by the company to identify resource use and costs for health states in the economic model. Section 4.2 describes the searches undertaken for the systematic reviews of cost-effectiveness studies, HRQoL studies and resource use/cost studies. The systematic review for costs identified three studies.[43, 44, 70]

The company used Willson and colleagues[44] as a template for their own model, and for model health state costs. Willson and colleagues contained seven live health states, while the company's model contains five live health states.[44] A comparison of the live health states between Willson and colleagues and the company's model (CS Table 119) is provided in Table 85.

Table 85 Comparison of live health state definitions in Willson et al and the CS model (CS Table 119, p.209)

Willson et al[44]	Current model
Controlled asthma: ACQ <1	**Controlled asthma:** Improved asthma: ACQ ≤1.5 (weight of 51%) Adequately controlled asthma identified as ACQ <1 (weight of 49%)
Partly-controlled asthma: 1≥ ACQ >1.5	
Uncontrolled asthma: ACQ ≥1.5	**Uncontrolled asthma:** ACQ ≥1.5
Non-severe exacerbation: The symptoms are outside the patient's usual range of day-to-day asthma and last for at least 2 consecutive days, and/or a decrease of PEF of ≥30.	**Moderate exacerbation:** Worsening of symptoms including unscheduled physician visit but no (additional) use of systemic corticosteroids.
Severe exacerbation without hospitalisation: Non severe exacerbation + corticosteroids (at least 3 days)	**Severe exacerbation:** Exacerbation requiring (additional) use of systemic corticosteroids and hospitalisation for 24.84% of these (estimate based on data provided by a UK expert, as described in CS Section 5.5)
Severe exacerbation with hospitalisation: Severe exacerbation + hospitalisation	

Abbreviations: ACQ: Asthma Control Questionnaire; ER: emergency room; GP: general practitioner; PEF: peak expiratory flow.

The CS indicates that costs were updated from Norman and colleagues[47] using 2015 PSSRU[8] and 2014/15 NHS Reference Costs, however, we were unable to confirm all codes in the 2014/15 NHS Reference Costs.[71] We requested clarification from the company via NICE on the derivation and calculation of the state costs used in the model. The costs analysed in this section consider the clarifications submitted by the company (clarification Appendix 4). Table 86 shows the unit costs for outpatient and home visits reported in the CS (CS Table 117). Unit costs for inpatient hospitalisations due to exacerbations, with information provided through clarification are reported in Table 87. The full tabulation of the unit costs are reported in Table 88. The bold and italicised values indicate the values that are used to calculate health state costs in the CS.

Table 86 NHS Reference and PSSRU unit costs used in the model

Resource	Cost	Code	Source
Outpatient visit to GP	£44.00	N/A	PSSRU 2015[68]
Outpatient visit to nurse	£14.47	N/A	(15.5 minutes) PSSRU 2015[68]
Home visit from GP	£113.00	N/A	(11.4 minute consultation, 12 minute travel) PSSRU 2015,[68] updated to 2016 using the health CPI[72]

GP, general practitioner; PSSRU, Personal Social Services Research Unit; N/A, not applicable

Table 87 NHS Reference Costs used to calculate health state costs[71]

Currency Code	Currency Description	Attendances	National Average Unit Cost
Hospitalisations[a]			
DZ15M	Asthma with Interventions	1,170	£2,634.34
DZ15N	Asthma without Interventions, with CC Score 9+	2,127	£1,907.15
DZ15P	Asthma without Interventions, with CC Score 6-8	5,752	£1,323.18
DZ15M/N/P	Weighted average asthma admissions CC 6-9+, and with interventions	9,049	***£1,629.97***
Ambulance[b]			
ASS01	See and treat or refer	2,270,229	***£179.83***
Accident and Emergency Visit[c]			
VB06Z	Emergency Medicine, Category 1 Investigation with Category 3-4 Treatment	347,157	***£132.38***
Intensive Care Unit[d]			

XC06Z	Adult Critical Care, 1 Organ Supported	553,390	***£937.65***

[a]Total HRGs Schedule, there are 2 further less severe codes, DZ15Q and DZ15R
[b]Ambulance (AMB) Schedule, assumes no patients conveyed to hospital (Currency Code ASS02)
[c]Emergency Medicine (EM) schedule, this is the only value in T01NA Service Code that matches. The choice is not explained in the CS,many other values could have been chosen.
[d]Total HRGs Schedule, other numbers of organs could be supported, no justification provided for this parameter choice

Unlike Willson and colleagues, [44] the company's model does not consider the costs of rescue medications, as the company considered these costs to be negligible and uncertain. We agree that costs for medications associated with hospitalisations were negligible and find the company approach reasonable with regards to these medications. In Willson and colleagues, co-medication accounted for at most 0.56% of weekly costs.[44]

For the Controlled asthma state in the CS model, a weighted average of patients in the Controlled asthma and Partly controlled asthma' states in Willson and colleagues was used based on ACQ levels in the pivotal trials,[19] just as was used in utility values (see Section 4.3.6.2). According to the definition used in Willson and colleagues, patients in the pivotal reslizumab trials had 'Partly controlled asthma' 49% of the time.

Table 88 Inpatient health state costs for exacerbations (CS Table 117, p. ~~205~~ 206)

Resource	Cost	Code	Source
Severe exacerbation-related hospitalisation	£1,629.97	DZ15M/N/P[†]	NHS reference costs schedule – 2014/2015[71]
A&E visit only	£132.38	VB06Z	
A&E visit + hospitalisation	£1,761.97	VB06Z + DZ15M/N/P[†]	
Ambulance + hospitalisation	£1,809.80	DZ15M/N/P[†] + ASS01 (ambulance)	
Ambulance + A&E + hospitalisation	£1,941.80	ASS01+ VB06Z + DZ15M/N/P[†]	
Hospitalisation including ICU stay	£2,567.62	DZ15M/N/P[†] + XC06Z (ICU stay)	

Abbreviations: A&E: Accident and Emergency; ICU: intensive care unit;[†]Average of the unit costs of three different codes that depend on severity of exacerbation.

Healthcare resource use was estimated using values from Willson and colleagues with updated costs applied to these resource use values.[44] The mean cost of severe exacerbation was a

weighted cost of severe exacerbations leading and not leading to hospitalisation. The percentage of severe exacerbations requiring hospitalisation was estimated at 24.84% based on data provided by a UK expert consulted by the company.

In order to calculate health state costs per cycle for the moderate exacerbation state, the company assumed that patients having a moderate exacerbation had one week of exacerbation and three weeks of uncontrolled asthma. For patients having a severe exacerbation, the time in the exacerbation states was two weeks, with two weeks in the uncontrolled asthma state.

Table 89 reports the health state costs values reported in the CS report, but these do not match the numbers used in the model, so we requested clarification from the company. Values that differ or were omitted from health state cost calculations in the clarification data provided by the company (Updated model provided at clarification) are displayed using italicized and bold font. The clarification data provided were marked as CiC. The table also shows the differences in health state costs where the resource use values in CS Table 120 are used for health state calculations (penultimate row), or where the resource use values in the confidential data submitted by the manufacturer are used to calculate health state costs (final row).

Table 89 Health state costs, adapted from CS Table 120 (p. 211) (values in parentheses are CiC data submitted by the company)

		Weekly resource use (n)			
		Controlled Asthma	**Uncontrolled Asthma**	**Moderate exacerbation**	**Severe exacerbation**
Outpatient visits					
Visit to GP	£44.00	0.035	0.14	0.6	0.6302
Visit to nurse	£14.47	0.059	0.16	0.43	0.5139
Visit to specialist	£133.26	***0.0243 (***[redacted]***)***	***0.094 (***[redacted]***)***	***0.094 (***[redacted]***)***	***0.2899 (***[redacted]***)***
Home visit					
Visit from GP	£112.95	0.00507	0.025	0.034	***0.1907 (***[redacted]***)***
Visit from nurse	£37.33	0	0	0	***0.0047 (***[redacted]***)***
Laboratory tests/procedures					
Spirometry	£28.20	***0.027 (***[redacted]***)***	***0.049 (***[redacted]***)***	***0.29 (***[redacted]***)***	***0.46 (***[redacted]***)***
Flu vaccine	£6.32	***0.02 (***[redacted]***)***	***0.02 (***[redacted]***)***	0	0

Desensitisation	£175.32	***0.00612 (***[redacted]***)***	***0.0087 (***[redacted]***)***	0	0
Inpatient resource use (from the clinical trials)					
Hospitalisation	£758.98	0	0	0	0
Severe exacerbation	£1,629.97	0	0	0	0.0242
A&E visit only	£132.00	0	0	0	0.0218
A&E visit + hospitalisation	£1,761.97	0	0	0	0.0255
Ambulance + hospitalisation	£1,809.80	0	0	0	0.0014
Ambulance + AE + hospitalisation	£1,941.80	0	0	0	0.0027
Hospitalisation including ICU stay	£2,567.62	0	0	0	0.0081
Weekly total		£8.17	£26.86	£57.17	£224.31
Cycle total (4 weeks)		£32.66	£107.44	£137.74	£897.25
CS Model Health State costs		£11.86	£45.19	£70.36	£649.56

When all costs listed in CS Table 120 are included at the reported values instead of the CiC values received during clarification, costs significantly increase for all states. The health state costs calculated using the reported values in CS Table 120 are between 1.38 and 2.75 times higher than the health state costs used in the model. We have conducted a sensitivity analysis that uses the cycle total costs reported in Table 88 (see section 4.4).

4.3.8 Model validation and consistency

The CS reports (CS page 193) that UK clinical experts were consulted for advice on the model structure, discontinuation rules, the target population, health care resource use, health care utility values, and the approach used to estimate transition probabilities. The CS does not report any internal consistency checks on the model for data inputs, any testing of the model, or details of which experts were consulted.

The economic model is coded in Microsoft Excel and is fully executable. Parts of the model are coded in visual basic macros which hinders transparency. We have not undertaken a comprehensive check of all cells in the model; rather, internal consistency checks have been performed and random checking of the model has been done for some of the key equations in the model. We have performed a detailed checking of all model inputs reported in the CS (white box testing); changing the parameter values produced intuitive results (black box testing) and from random checking the 'wiring' of the model appears to be accurate. The ERG was able to replicate the results presented in the CS and the deterministic sensitivity analyses, as reported in CS Figure 52 and CS Figure 53. We view the model as a reasonable approach to modelling the cost effectiveness of severe eosinophiliic asthma.

The company provided a revised model to NICE because they had discovered errors in the PSA and in the costing of omalizumab. The company stated that for the PSA:

[redacted]

The following errors were identified by the company and corrected in the revised model for the omalizumab treatment arm as reported below:

[redacted]

The CS presents a validation of the risk of exacerbations to verify the assumption that a common multiplier can be applied to all probabilities of transitioning to the exacerbation health states. The model was run by the company using the transition probabilities for patients having experienced ≥ 2 exacerbations in the previous year with a exacerbation multiplier of 1. The rate of exacerbations in the BSC arm was 2.06 compared with 0.93 in the reslizumab arm, i.e. reslizumab decreased the number of moderate and severe exacerbations by 50% and 53% respectively (CS Table 145 and Table 90 of this report).

Table 90. Clinical outcomes from the company model for patients having experienced 2≥ exacerbations in the 3082 and 3083 trials (multiplier=1)

	Time controlled (years)	Time un-controlled (years)	# of moderate exacer-bations	# of severe exacer-bations	Deaths due to asthma	Exacer-bation rate
Reslizumab (total)	17.77	14.07	6.06	25.78	0.16	0.93
On treatment	13.24	7.60	1.16	3.72	0.02	0.23
Off treatment	4.54	6.47	4.91	22.05	0.15	2.06
BSC	11.27	16.08	12.20	54.84	0.30	2.06
% difference	58%	-13%	-50%	-53%	-46%	-55%

The company does not comment on how this analysis confirms that the common multiplier is justified but the ERG notes that the exacerbation rate for reslizumab and BSC in this analysis are consistent with the clinically significant exacerbation rate estimates from trials 3082 and 3083 (see Table 18 of this report). The company also conducted an analysis based on all adult patients at GINA steps 4/5 with a multiplier of 1.535 applied to the transition probabilities. The results for this analysis are reported in CS Table 146 and show similar results to the analysis for patients having experienced ≥2 exacerbations in the previous year.

We note that the validation for the rate of exacerbations in the BSC arm was conducted using patients with ≥2 exacerbations with a multiplier of 1. However, for the base case analysis the company used patients with ≥3 exacerbations with a multiplier of 2.15. For the base case the rate of moderate and severe exacerbations is 4.3, which is about double that seen in the pivotal clinical trials. The ERG therefore considers that the base case analysis is overestimating the

BSC exacerbation rate. The rate of exacerbations is investigated in ERG additional analyses (section 4.4).

The company states that they validated their results against existing cost effectiveness studies, where possible. The model developed by Faria and colleagues[73] reported total QALYs of 14.13 and 13.66 over a patient's lifetime for omalizumab and BSC, compared to the company's results of 12.85 and 11.23. The company considers that the results in their model are in line with those of Faria and colleagues and notes that the analyses are for different populations as Faria and colleagues considered patients in GINA step 5 without any restriction on the baseline risk of exacerbations.

4.3.9 Cost effectiveness Results

Deterministic results from the economic model are presented (CS section 5.7) as the incremental cost per QALY gained for reslizumab compared with BSC. The company sent a revised model with changes for the comparison with omalizumab. Results are also reported for total life years. The company analyses and the ERG analyses in this report are for the list price for omalizumab and the PAS price for resilizumab.

For the base case, CS Table 124 reports an incremental cost effectiveness ratio (ICER) gained of £24,907 per QALY for reslizumab versus BSC (as shown in Table 91). The comparison with omalizumab is for the population of patients with severe persistent allergic IgE-mediated asthma and a history of ≥3 exacerbations (

Table 92).

Table 91 Deterministic base case cost effectiveness results for patients with a history of ≥3 exacerbations

Treatment arm	Total			Incremental			ICER/ QALYs, £
	Costs, £	LYG	QALYs	Costs, £	LYG	QALYs	
BSC	[redacted]	[redacted]	[redacted]				
Reslizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,907

Table 92 Deterministic base case cost effectiveness results for patients with persistent allergic eosinophilic asthma and a history of ≥ 3 exacerbations (CS Table 125, page 219)

Treatment arm	Total			Incremental			ICER/ QALYs, £ increment	ICER/ QALYs, £ vs BSC
	Costs, £	LY	QALYs	Costs, £	LYG	QALYs		
BSC	[redacted]	[redacted]	[redacted]					
Omalizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated[a]	£33,254
Reslizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,907	£24,907

[a] An extendedly dominated intervention has an ICER higher than that of the next most effective intervention.

The CS summarises the results of the PSA stating, at a threshold willingness to pay of £20,000 and £30,000 per QALY gained (in the revised model), that there is a [redacted] and [redacted] probability of reslizumab being cost-effective respectively.

The CS states that the results show that reslizumab is a cost effective add-on therapy to BSC for adult patients with severe eosinophilic asthma who are uncontrolled despite high-dose ICS.

4.3.10 Assessment of uncertainty

The company conducted deterministic sensitivity analyses for 50 input parameters. These included time horizon, discount rate, health state costs, utilities, patient age, exacerbation rate, relative risk of exacerbations and mortality risk (CS Table 135). The company varied the parameters using the 95% confidence intervals as upper and lower values. Where these were not available (or where the variability was thought to be greater than in the study source), parameters were varied by +/-20%.

Tornado diagrams are presented of the deterministic sensitivity analyses for reslizumab vs BSC in CS Figure 52 (reproduced in Figure 9 and Figure 10 of this report). The tornado diagram for reslizumab vs omalizumab was from the revised model submitted by the company.

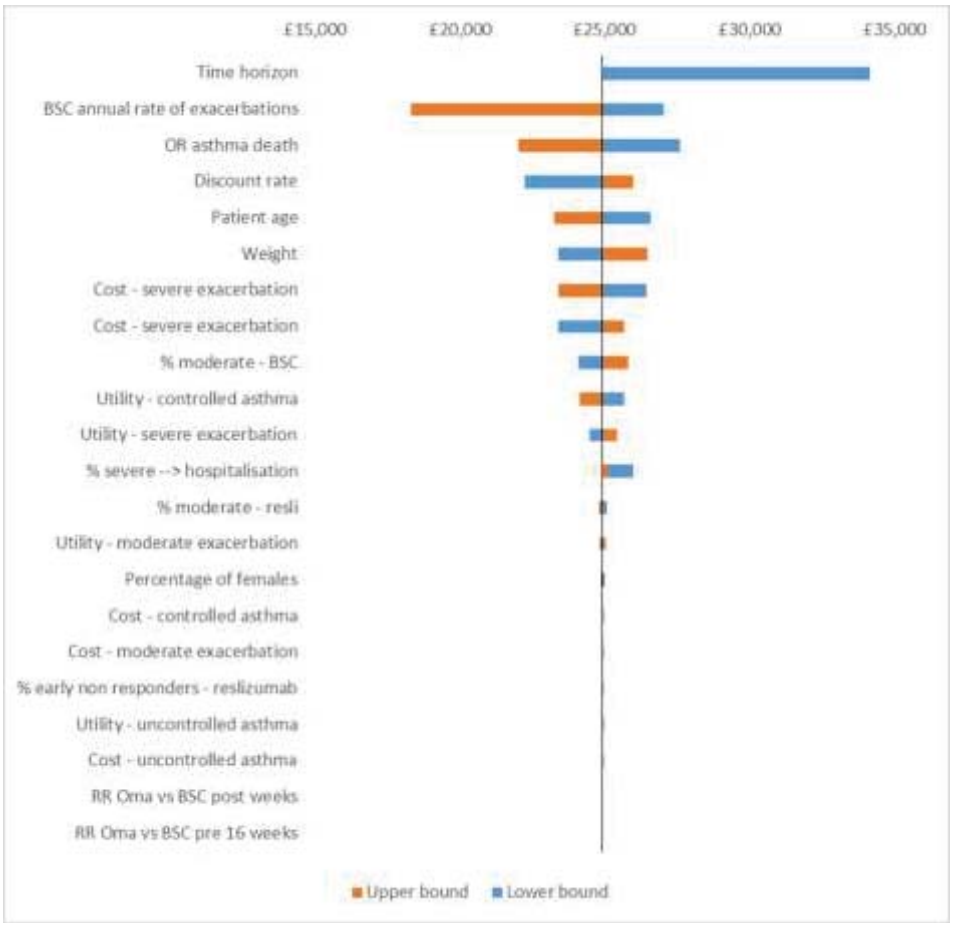


Figure 9 Tornado diagram: deterministic sensitivity of resilzumab vs BSC

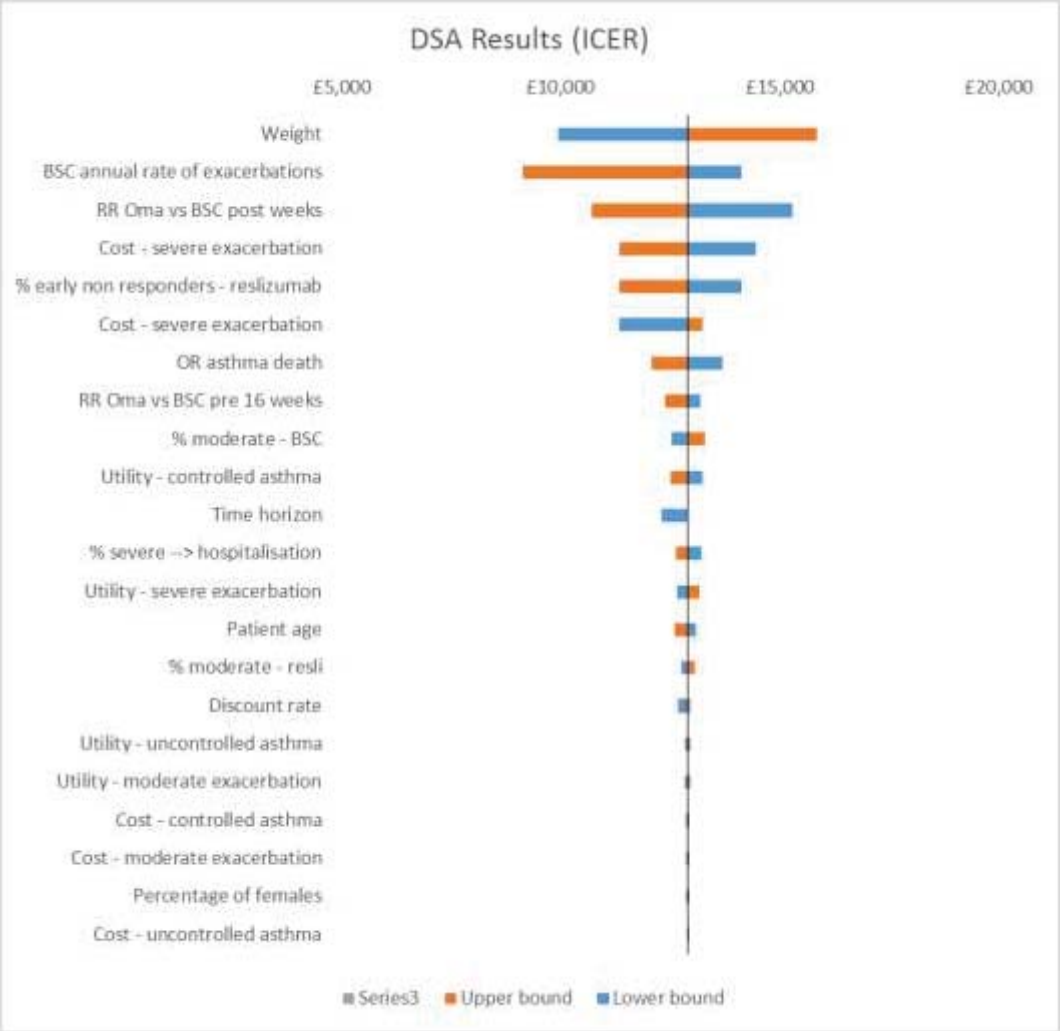


Figure 10 Tornado diagram: deterministic sensitivity of resilzumab vs omalizumab (from company's revised model)

The deterministic sensitivity analyses for reslizumab vs. BSC found that results were most sensitive to changes in the baseline risk of exacerbations, a shorter time horizon and the risk of asthma death. For the deterministic sensitivity analyses for reslizumab vs. omalizumab, the results were most sensitive to risk of exacerbation, patient weight and the relative risk of exacerbation for omalizumab versus BSC.

Scenario analyses

The company conducted six scenario analyses that investigated the use of 100mg vials, alternative utility data sources, and reducing the omalizumab price. These analyses are shown in the CS in Tables 137-138 and in the revised model for omalizumab discount prices (summarised here in Table 93).

The company states that it conducted a scenario analysis for the use of 100mg vials because this is the size in which reslizumab is currently available. The base case analysis uses 25mg vials which are expected to be available in [redacted]. Using 100mg vials with no vial sharing increases the ICER to £32,330 per QALY.

Table 93 Scenario analyses

Scenario	Comparison, Reslizumab vs.	ICER (£/QALY)
Use of 100mg vial : no vial sharing	BSC	£32,330
Use of 100 mg vial: vial sharing	BSC	£23,189
Use of uncontrolled and controlled asthma utilities	BSC	£25,839
20% discount of omalizumab list price	Omalizumab	Omalizumab extendedly dominated
30% discount of omalizumab list price	Omalizumab	£24,420
40% discount of omalizumab list price	Omalizumab	£28,264

The company conducted a scenario analysis with alternative utility values for the controlled and uncontrolled asthma health states. These data were from a mapping of patient HRQoL data collected from the pivotal clinical trials using AQLQ scores. The company did not supply the utility values used in this scenario. Using alternative utility values increased the ICER to £25,839 per QALY.

Omalizumab is provided to the NHS with a confidential patient access scheme (PAS). Scenario analyses were conducted varying the assumed PAS for omalizumab in the revised model between 20% and 40% and the ICER varied between £20,576 and £28,264 per QALY. The ERG presents model results with the PAS price in a confidential appendix to this report.

Subgroup analyses

The CS reports subgroup analyses for different populations for reslizumab compared to BSC (CS Tables 142 – 144). The subgroup analyses corresponded to the number of exacerbations experienced in the year preceding enrolment in the clinical trials, with analyses presented for patients having experienced ≥2 and ≥4 and for adult patients classified as GINA 4/5. For these analyses, the company applied the exacerbation multiplier that produced the expected number of exacerbations in the BSC arm (i.e. 2.32 exacerbations in patients having experienced at least 2 exacerbations; 5.61 exacerbations for patients having experienced at least four exacerbations, and 1.98 exacerbations in adult patients classified as GINA 4/5. For the analysis with patients having experienced ≥2 exacerbation the ICERs was £33,774 per QALY, whilst for those having

experienced ≥4 exacerbation the ICER was £20,006 per QALY respectively. For the analysis with adult patients classified as GINA step 4/5, the ICER was £52,738 per QALY.

Probabilistic sensitivity analysis

The company performed PSA with 1000 iterations with the distributions used for the input parameters shown in CS Tables 131 and ~~131~~ 132. The company varied the input parameters in the deterministic sensitivity analyses and also the transition probabilities. The model used the gamma distribution to vary costs, and the beta distribution for utilities and transition probabilities. A log-normal distribution was used for the relative risk of exacerbation versus BSC and the risk of asthma-related mortality. The uniform distribution was assumed for the percentage of severe exacerbations, the proportion of moderate exacerbations and percentage of early responders.

The company provided a revised model. The PSA results are shown in Appendix 4 of the company's clarification response. The PSA results are similar to the deterministic results (Table 94).

The CS states that the transition probabilities were drawn independently for reslizumab and BSC which leads to higher levels of uncertainty. The ERG agrees that the transition probabilities should be correlated between those for reslizumab and BSC and sampling them independently incorporates higher levels of uncertainty in the PSA results.

Table 94 Mean PSA results (from revised company model)

	Reslizumab vs. BSC		Reslizumab vs. omalizumab	
	Base case	PSA	Base case	PSA
Mean ICER	£24,907	[redacted]	[redacted]	£12,537

The CS reports cost effectiveness acceptability curves for reslizumab versus BSC (Appendix 4 in the company's clarification response) and for reslizumab versus omalizumab for patients with severe persistent allergic IgE-mediated asthma. At thresholds for willingness to pay of £20,000 and £30,000 per QALY gained, that there is a [redacted] and [redacted] probability of reslizumab being cost-effective respectively. A cost effectiveness acceptability curve for reslizumab versus BSC and omalizumab from the revised model is shown here in XXXXXXX11 .

11

4.4 Additional work undertaken by the ERG

This section details the ERG's further exploration of the issues and uncertainties raised in the review and critique of the company's cost effectiveness analyses. This consists of additional sensitivity analyses for the exacerbation rate of BSC, utilities and the cost of exacerbation, using the company's revised model. The results are shown comparing reslizumab to omalizumab and to BSC; the comparison against omalizumab is for patients with severe persistent allergic IgE-mediated eosinophilic asthma.

The company base case results used transition probabilities from the population with patients who had more than ≥ 2 exacerbations in the previous year with an exacerbation multiplier of 2.15, to reflect the rates of exacerbation. Unless stated otherwise, this set of transition probabilities has been used in the ERG analyses.

i) Exacerbation rate of BSC

As discussed in section 4.3.8 of this report, we observed that the base case analysis overestimates the BSC exacerbation rate. We considered that the exacerbation multiplier

should be 1, rather than 2.15 as used in the base case. The company included this analysis as a validation analysis and the clinical outcomes are shown in section 4.3.8.The ERG run the model with a multiplier of 1 and the results are shown for reslizumab versus BSC and omalizumab in Table 95. Using a multiplier of 1 increases the ICER to £50,878 per QALY for reslizumab versus BSC.

We also conducted an analysis using transition probabilities for patients classified as being at GINA steps 4/5 with a multiplier of 1.535, which produced an annual exacerabation rate of 2.06. This produced an ICER of £51,240 per QALY for reslizumab compared to BSC.

Table 95 ERG analyses for patients with changes to exacerbation multiplier

Scenario	Treatment	Total costs	Total QALYs	Incremental ICER (£/QALY)
Base case, Patients with history ≥2 exacerbations of multiplier = 2.15	BSC	[redacted]	[redacted]	
	Omalizumab	[redacted]	[redacted]	Extendedly dominated
	Reslizumab	[redacted]	[redacted]	£24,907
Patients with history of ≥2 exacerbations, multiplier = 1	BSC	[redacted]	[redacted]	
	Omalizumab	[redacted]	[redacted]	Extendedly dominated
	Reslizumab	[redacted]	[redacted]	£50,878
Patients classified as GINA 4/5, multiplier = 1.535	BSC	[redacted]	[redacted]	
	Omalizumab	[redacted]	[redacted]	Extendedly dominated
	Reslizumab	[redacted]	[redacted]	£51,240

ii) Utility values

In these three scenarios, the model was run with alternative utility values, shown in Table 96. As described in section 04.3.6, the method used for utility measurement differed between the company's model and the NICE MTA for omalizumab. The company used the absolute values for the exacerbation health states from the study from Lloyd and colleagues, whilst Norman and colleagues[73] used disutilities from Lloyd and colleagues that are applied to treatment states using a difference form baseline approach. We undertook as similar approach to Norman and colleagues, applying the disutilitiies from Lloyd and colleagues to the uncontrolled health state to derive the exacerbation utility values (utility scenario 1). An alternative approach (utility scenario 2) is to use ratios to represent changes in utility from baseline for exacerbation compared to uncontrolled health states.

We noted that the utility value for severe exacerbations in the study by Lloyd and colleagues was defined where all patients in this state were hospitalised and the definition for severe exacerbation in the CS included a proportion (23%) who were hospitalised and the remainder who were not hospitalised. We recalculated the utility value for the severe exacerbation health state by calculating a weighted average with those who were hospitalised assigned the severe utility value and those who were not hospitalised assigned the moderate exacerbation utility value. The model was run with this value for severe exacerbations (utility scenario 3).

Table 96 Utility values used in the CS base case and the ERG utility scenarios

Health State	Ratio to baseline	Base case[a]	Utility Scenario 1[b]	Utility Scenario 2[c]	Utility scenario 3[d]
Uncontrolled utility	1.000	0.728	0.728	0.728	0.728
Moderate exacerbation	0.850	0.570	0.628	0.619	0.570
Severe exacerbation	0.623	0.330	0.528	0.453	0.510

[a] Absolute utility scores from Lloyd and colleagues for exacerbations
[b] Change from baseline from Lloyd and colleagues, as in Norman and colleagues
[c] Utility scores calculated as a ratio to baseline
[d] Utility scores for severe exacerbation reweighted according to the proportion hospitalised

The results for reslizumab compared to BSC and to omalizumab are shown in Table 97. The ICER increases for the utility scenarios to £30,717, £28,302 and £29,720 per QALY for utility scenarios 1, 2 and 3 respectively for reslizumab compared to BSC.

Table 97 ERG analyses with changes to the utility values

Scenario	Treatment	Total costs	Total QALYs	Incremental ICER (£/QALY)
Base case	BSC	[redacted]	[redacted]	
	Omalizumab	[redacted]	[redacted]	Extendedly dominated
	Reslizumab	[redacted]	[redacted]	£24,907
Utility scenario 1;	BSC	[redacted]	[redacted]	
	Omalizumab	[redacted]	[redacted]	Extendedly dominated
	Reslizumab	[redacted]	[redacted]	£30,717
Utility scenario 2;	BSC	[redacted]	[redacted]	
	Omalizumab	[redacted]	[redacted]	Extendedly dominated
	Reslizumab	[redacted]	[redacted]	£28,302
Utility scenario 3;	BSC	[redacted]	[redacted]	
	Omalizumab	[redacted]	[redacted]	Extendedly dominated
	Reslizumab	[redacted]	[redacted]	£29,720

iii) Health state costs

We noted that there were some inconsistencies in the reporting of the health state costs (section 151). We have recalculated these costs (Table 98). A scenario analysis was undertaken with these health state costs and is shown in Table 99. The revised health state costs decrease the ICER for reslizumab compared to BSC by about £1300.

Table 98 Health state costs, adapted from CS Table 120

	Weekly resource use (n)			
	Controlled Asthma	Uncontrolled Asthma	Moderate exacerbation	Severe exacerbation
CS Model Health State costs (4 weeks)	£11.86	£45.19	£70.36	£649.56
ERG revised health state costs (4 weeks)	£32.66	£107.44	£137.74	£897.25

Table 99 ERG analyses with changes to the health state cost values

Scenario	Treatment	Total costs	Total QALYs	Incremental ICER (£/QALY)
Base case	BSC	[redacted]	[redacted]	
	Omalizumab	[redacted]	[redacted]	Extendedly dominated
	Reslizumab	[redacted]	[redacted]	£24,907
Revised health state costs	BSC	[redacted]	[redacted]	
	Omalizumab	[redacted]	[redacted]	Extendedly dominated
	Reslizumab	[redacted]	[redacted]	£22,278

iv) Monitoring costs

We noted that the monitoring times used for omalizumab in the previous NICE MTA appraisal for omalzimuab (15 minutes) differed from the time used in the current appraisal (30 minutes). We conducted an analysis using the monitoring time used in these appraisals. ~~*The results are shown in Table 100 for reslizumab compared to omalizumab where the ICER increases to £26,390 per QALY.*~~ *We conducted an analysis using the monitoring time used in these appraisals. The costs of omalizumab are reduced by about £2000 (Table 100).*

Table 100 ERG analyses with changes to the monitoring duration for omalizumab

Scenario	Treatment	Total costs	Total QALYs	Incremental ICER (£/QALY)

Base case	BSC	[redacted]	[redacted]	
	Omalizumab	[redacted]	[redacted]	Extendedly dominated
	Reslizumab	[redacted]	[redacted]	£24,907
Revised monitoring duration	BSC	[redacted]	[redacted]	
	Omalizumab	[redacted]	[redacted]	~~£23,302~~ Extendedly dominated
	Reslizumab	[redacted]	[redacted]	~~£26,390~~ £24,907

The ERG's preferred base case

We conducted an analysis that combined the ERG scenarios above comprising: change in exacerbation rate for BSC (exacerbation multiplier =1), utility scenario 1, change in health state costs and change in monitoring duration for omalizumab. The results for the ERG's preferred base case (Table 101) show an ICER of £57,602 per QALY for reslizumab compared to omalizumab.

The ERG's preferred base case analysis was repeated for the alternative set of transition probabilities for adult GINA steps 4/5 patients, with a multiplier of 1.535. For this analysis, the ICER for reslizumab compared to BSC is £57,602 per QALY.

Table 101 ERG preferred base case analyses

Scenario	Treatment	Total costs	Total QALYs	Incremental ICER (£/QALY)
Base case	BSC	[redacted]	[redacted]	
	Omalizumab	[redacted]	[redacted]	Extendedly dominated
	Reslizumab	[redacted]	[redacted]	£24,907
ERG preferred base case; Patients ≥ 2 exacerbations; multiplier = 1	BSC	[redacted]	[redacted]	
	Omalizumab	[redacted]	[redacted]	Extendedly dominated
	Reslizumab	[redacted]	[redacted]	£57,356
ERG preferred base case; Patients GINA4/5; multiplier = 1.535	BSC	[redacted]	[redacted]	
	Omalizumab	[redacted]	[redacted]	Extendedly dominated
	Reslizumab	[redacted]	[redacted]	£57,602

4.5 Conclusions on cost effectiveness

The company adapted a model structure published by Willson and colleagues that compared tiotropium bromide to BSC in patients with severe asthma.[44] The company does not provide a rationale for the choice of model structure, but the ERG considers the model structure to be appropriate for the decision problem. The structure of the model is different from the models used for technology appraisals of omalizumab and mepolizumab, and other published models.[44, 47, 48] The differences in model structure make comparison of the model results difficult.

The company used methods that are consistent with NICE methodological guidelines. The population, intervention and comparators used in the economic evaluation are broadly consistent with the NICE scope. What was considered as part of BSC was not well defined in the scope or in the model; in practice, BSC could incorporate a number of treatments and it is unclear if different treatments in the asthma care pathway may be more effective than others.

The core clinical evidence for reslizumab was derived from several large, good quality trials,[19] that compared reslizumab to BSC. The model uses transition probabilities according to the transitions observed in the trial, however the ERG had concerns over the explanation of the derivation of the transition probabilities and the rationale for choosing to use the subgroup of patients with more than 2 previous exacerbations. Further the ERG questions whether it is appropriate to calibrate the model to increase the number of exacerbations, to a similar level as seen in the year preceding the trial.

The results in the CS and in this report are presented for the list price for omalizumab and the confidential PAS price for resilizumab. The CS base case analysis comparing reslizumab to BSC had an ICER of £24,907 per QALY. The base case ICER for reslizumab compared to omalizumab and BSC in patients with persistent allergic eosinophilic asthma and a history of ≥3 exacerbations was also £24,907 per QALY, as omalizumab was extendedly dominated (a combination of BSC and reslizumab would be more cost-effective than offering omalizumab). The ICER for omalizumab compared to BSC is £33,254 per QALY, which is more than the ICER for reslizumab compared to BSC. The company's PSA indicated that at a threshold of £20,000 per QALY there would be a [redacted] probability that reslizumab is cost-effective and at £30,000 per QALY this probability increases to [redacted]. In addition to PSA, a wide variety of one-way deterministic sensitivity analyses were conducted.

Generally, sensitivity analyses showed that results were most sensitive to assumptions about exacerbations. The number of exacerbations in trial subgroups was positively correlated with reslizumab cost-effectiveness.

The ERG has some concerns about choices of parameters, and conducted analyses evaluating lower rates of exacerbations in the BSC arm, alternative methods of calculating exacerbation utility scores, different cost for administration of omalizumab, and different health state costs based on the values reported in the CS rather than the values used in the model.

The ERG's alternative base case analysis for the comparison for reslizumab compared to BSC produces an ICER of £57,356 per QALY. In comparison to reslizumab, omalizumab remains extendedly dominated.

5 Innovation

The company claims (CS section 2.5) that reslizumab is an innovative therapy, since:

(1) There are currently very few treatment options for patients with severe (BTS/SIGN and GINA Step 4/5) asthma with elevated eosinophils who are not eligible for omalizumab treatment and remain inadequately controlled on best standard of care (BSC), other than continuing to increase the ICS dose or adding OCS.

(2) No other biologic therapies with the same mode of action as reslizumab (i.e. high-affinity binding to IL-5 to reduce eosinophil maturation, survival and activity are currently available).

The ERG agrees that these are reasonable claims, although we note, as the company mentions, that the anti-IL-5 monoclonal antibody mepolizumab is licensed as an add-on treatment for severe refractory eosinophilic asthma in adults, but is not currently recommended by NICE (appraisal ongoing).

6 DISCUSSION

6.1 Summary of clinical effectiveness issues

The CS and the ITC Report, although generally well structured, contain numerous inconsistencies, many of which may be typographical errors. This makes the submission difficult to follow and appraise accurately. Sample sizes reported for the trials are inconsistent both within the CS and between the CS and that ICS Report, and for most of the outcomes analysed the reported sample sizes suggest that an ITT analysis was not followed. Feasibility assessments for the inclusion or exclusion of trials for both the direct comparison meta-analysis and ITC are not clearly explained, and the CS presents a confusing picture as to whether trial Res-5-0010 is relevant or not. The company makes a key assumption that placebo and BSC are equivalent without providing any justification for this and without mentioning whether the assumption is robust to placebo effects. The ITC Report also fails to mention that not all omalizumab trials had a placebo or BSC comparator and it is unclear whether 'optimised asthma control' or 'control group' arms in omalizumab trials are equivalent to BSC.

The ERG has ~~*a number of*~~ further concerns about the company's ITC. ~~*For the AQLQ outcome assessed at 16±4 weeks the trial Res-5-0010 is included in the ITC of reslizumab versus omalizumab but excluded from the direct comparison of reslizumab versus placebo, without any explanation.*~~ ~~*Second, the*~~ The company's process for selecting trials based on their definitions of clinically significant exacerbations appears inconsistent, meaning that several omalizumab trials may have been unnecessarily excluded from analysis. ~~*The ITC Report selectively presents only fixed-effects model results for the analysis of clinically significant exacerbation rates when a random-effects analysis should at least have been presented for comparison.*~~

[Note added after final submission of this ERG report to NICE: The company clarified during the factual inaccuracy check process that sample sizes for the ITC analyses were the same as those for their direct comparison meta-analysis but were reported incorrectly in the ITC Report (the ERG cannot corroborate this). The company also clarified that trial Res-5-0010 was not included in the AQLQ ITC analysis, although the ITC Report states that it was. These discrepancies do not materially affect the conclusions of this report, since other uncertainties in the results of the ITC analysis remain].

6.2 Summary of cost effectiveness issues

The CS includes evidence on the cost-effectiveness of reslizumab compared to BSC and omalizumab for severe asthma. The model structure adopted for the economic evaluation is generally appropriate and consistent with the clinical disease pathway. The model uses transition probabilities according to the transitions observed in the pivotal clinical trials, however the ERG had concerns over ~~the explanation of the derivation of the transition probabilities and~~ the rationale for choosing to use the subgroup of patients with more than 2 previous exacerbations. Further the ERG questions whether it is appropriate to calibrate the model to increase the number of exacerbations, to a similar level as seen in the year preceding the trial.

The CS and this report present all results at the list price for omalizumab and the confidential PAS price for resilizumab. The model results suggest that reslizumab has a cost effectiveness versus BSC of £24,907 per QALY (omalizumab was extendedly dominated by BSC). The company conducted deterministic sensitivity analyses for the input parameters that found that the results were most sensitive to changes in the baseline risk of exacerbation, a shorter time horizon and the risk of asthma death.

The company's probabilistic sensitivity analyses showed there is a probability of [redacted] and [redacted] that reslizumab is cost effective at a willingness to pay threshold of £20,000 and £30,000 respectively.

The ERG conducted sensitivity analyses evaluating lower rates of exacerbations in the BSC arm, alternative methods of calculating exacerbation utility scores, different costs for the administration of omalizumab, and different health state costs based on the values reported in the CS rather than the values used in the model. The ERG's alternative base case analysis for the reslizumab compared to BSC produces an ICER of £57,356 per QALY.

A possible limitation of the economic analysis is that there was no evidence available from the trials or other data sources on a likely effect of reslizumab on oral steroid use. Use of oral corticosteroids is one of the outcome measures indicated for consideration in the NICE scope. Clinical experts advising the ERG noted that this is potentially an important factor, as, in addition

to their impact on adverse events, oral steroids are a significant cost driver in populations with severe asthma. Whilst exacerbations are clearly of key importance, they do not fully capture the potential cost-effectiveness of the intervention without including reductions in day-to-day symptoms and steroid requirements.

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Reslizumab for treating asthma with elevated blood eosinophils inadequately controlled by inhaled corticosteroids

Cover sheet for the ERG Report indicating the ERG's amendments made in response to the company's factual inaccuracy check

Produced by Southampton Health Technology Assessments Centre

Date completed 11th October 2016.

[redacted]

The following amendments have been made to the ERG report and are indicated within the report by *underlined italicised text*.

Page 11. The words "in this report" have been added to clarify that the ERG report refers to trials 3082 and 3083 as being the company's pivotal trials. This amendment addresses Issue 2 raised by the company (that the ERG's and company's references to 'pivotal' trials are slightly different). The ERG refers to these two trials as 'pivotal' given that they had longer duration than the other trials and were the key trials which informed the company's economic analysis.

Page 13. Changes in the second and third paragraphs have been made to clarify the number of trials which provided results for discontinuations due to adverse events and serious adverse events at 52 weeks (Issue 4 raised by the company). Results for serious adverse events at 16±1 weeks which were omitted from this summary have been added in the third paragraph (Issue 5 raised by the company).

Page 15. The second paragraph has been amended to clarify that the company reported a random-effects analysis for this outcome (Issue 6 raised by the company). This analysis was inadvertently missed by the ERG as it is given separately in an appendix and not discussed by the company in their submission.

Page 19. Third paragraph: missing CIC marking of probability values has been provided (Issue 7 raised by the company).

Page 21. The first bullet point has been amended to correct a company error wherein the company stated incorrectly that trial Res-5-0010 was included in the AQLQ outcome ITC analysis (Issue 1 raised by the company – not an ERG error). The fifth bullet point has been deleted, to remove an incorrect ERG statement that the company did not present a random-effects analysis for clinically significant exacerbations (Issue 6 raised by the company). A new final bullet point has been added to explain that, after the ERG report submission, the company acknowledged errors in the sample sizes reported for their ITC analysis (Issue 8 raised by the company – not an ERG error).

Page 40. Text has been amended to correct 'phase II' to read 'phase III' (Issue 10 raised by the company).

Pages 42-43. Table 4 has been amended so that exploratory variables are separated from secondary and tertiary variables in the Table (Issue 11 raised by the company). However this does not influence interpretation since the company does not define secondary, tertiary or exploratory variables.

Page 44. Text has been amended in the first paragraph to clarify that the company was aware of an imbalance in the proportion of females in the reslizumab arm of trial 3084 (Issue 12 raised by the company).

Page 49. Missing exacerbation proportions for trial 3084 have been added in Table 5 (Issue 13 raised by the company).

Page 54. A correction has been made to the cross-reference at the end of the second paragraph (Issue 14 raised by the company).

Page 59. Missing safety analysis sample sizes for trial 3084 have been added in Table 7 (Issue 15 raised by the company).

Page 62. A correction has been made to a cross-reference in the final paragraph (Issue 16 raised by the company).

Page 68. The third full paragraph has been deleted to correct a company error wherein the company stated incorrectly that trial Res-5-0010 was included in the AQLQ outcome ITC analysis (Issue 1 raised by the company – not an ERG error).

Page 82. In Table 24 the cited data source has been corrected from CS Table 59 to CS Table 60 (Issue 16 raised by the company).

Page 85. The final paragraph has been amended to provide a more precise description of the pattern of adverse events (Issue 17 raised by the company).

Page 88. An incorrect sample size value in Table 31 has been corrected (Issue 18 raised by the company).

Page 89. Text has been amended in the first paragraph to clarify the number of trials which reported discontinuations due to adverse events at 52 weeks (Issue 4 raised by the company). Table 32 has been amended to clarify that the 52-week results for serious adverse events are from trials 3082 and 3083 (Issue 5 raised by the company).

Pages 90-91. Table 34 and the paragraph above it, and Table 35, have been amended to provide missing results for three trials which reported serious adverse events up to 16±1 weeks (Issue 5 raised by the company).

Page 94. Table 40 has been amended to clarify that the means are least-squares means (Issue 20 raised by the company). To ensure consistency, standard means in the final row of the table have been replaced with least-squares means

Pages 95-96. Text at the end of page 95 and at the start of page 96 has been amended to clarify that the statistically significant change in ACQ score was in the total trial population, not in the subgroup analyses (Issue 21 raised by the company).

Pages 100-101. Table 46 and text in the first, second and third paragraphs on page 100 have been amended to clarify that the company reported a random-effects analysis for this outcome (Issue 6 raised by the company). This analysis was inadvertently missed by the ERG as it is given separately in an appendix and not discussed by the company in their submission.

Page 108. Table 61, and the text in the first and third paragraphs in section 3.4.5, have been amended to correct a company error wherein the company stated incorrectly that trial Res-5-0010 was included in the AQLQ outcome ITC analysis (Issue 1 raised by the company – not an ERG error).

Page 109. Text in the third paragraph has been amended to correct a company error wherein the company stated incorrectly that trial Res-5-0010 was included in the AQLQ outcome ITC analysis (Issue 1 raised by the company – not an ERG error).

Page 113. ‘AQLQ’ has been replaced with ‘HRQoL’ in the second bullet point (ERG typographic error). The third bullet point has been amended to correct a company error wherein the company stated incorrectly that trial Res-5-0010 was included in the AQLQ outcome ITC analysis (Issue 1 raised by the company – not an ERG error).

Page 114. The second bullet point has been deleted, to remove an incorrect ERG statement that the company did not present a random-effects analysis for clinically significant exacerbations (Issue 6 raised by the company).

Page 117. The number of excluded references has been corrected (Issue 22 raised by the company).

Page 131, 132, 134 and 138. An explanation has been added for why transition probabilities used in the model differed from the probabilities estimated directly from the clinical trials (Issue 23 raised by the company).

Page 153. A cross-reference in the caption of Table 88 has been corrected (Issue 16 raised by the company).

Page 159. First paragraph: missing CIC marking of probability values has been provided (Issue 7 raised by the company).

Page 163. A cross-reference in the first full paragraph has been corrected (Issue 16 raised by the company). An ICER in Table 94 has been corrected from [redacted] to [redacted] (Issue 24 raised by the company). In the last paragraph, missing CIC marking of probability values has been provided (Issue 7 raised by the company).

Page 164. Figure 11 has been marked as CIC (Issue 7 raised by the company).

Pages 167-168. In the Revised monitoring duration rows of Table 100 the total cost of reslizumab has been corrected from [redacted] to [redacted]; the corresponding ICER value has been updated to 'Extendedly dominated'; and the ICER value for reslizumab has been corrected from £26,390 to £24,907 (Issue 25 raised by the company).

Page 169. Fourth paragraph: missing CIC marking of probability values has been provided (Issue 7 raised by the company).

Page 171. Text in the second paragraph has been deleted to correct a company error wherein the company stated incorrectly that trial Res-5-0010 was included in the AQLQ outcome ITC analysis (Issue 1 raised by the company – not an ERG error). Text at the end of the second paragraph has been deleted, to remove an incorrect ERG statement that the company did not present a random-effects analysis for clinically significant exacerbations (Issue 6 raised by the company). A new final paragraph has been added to explain that, after the ERG report submission, the company acknowledged errors in the sample sizes reported for their ITC analysis (Issue 8 raised by the company – not an ERG error).

Page 172. Reference to ERG concerns over derivation of transition probabilities from the trial data has been removed (Issue 23 raised by the company). Third paragraph: missing CIC marking of probability values has been provided (Issue 7 raised by the company).

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Reslizumab for treating eosinophilic asthma inadequately controlled on inhaled corticosteroids [ID872]

You are asked to check the ERG report from Southampton Health Technology Assessment Centre to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, 29th September 2016** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Discrepancies regarding the exclusion of RES-5-0010 trial from SLR/meta-analysis Page 10 "The company stated that one of the reslizumab trials (Res-5-0010) was excluded from further consideration and the CS does not report any demographic details or quality assessment for this trial. However, the company subsequently included this trial in a number of outcome analyses."	Amend statement to: The reslizumab trial Res-5-0010 was included in the SLR, as well as in the direct comparisons and ITC when it reported on outcomes of interest. Demographic details and quality assessment for this trial can be found in the ITC Report's appendices.	The current statement is inaccurate and the demographic details and quality assessment for this trial can be found in the ITC Report's appendices: • Appendices 7, 8, and 9 of the ITC Report presents demographic details (baseline patient characteristics) of Res-5-0010 (Castro et al 2011) • Appendix 10 in the ITC Report presents the quality assessment for Res-5-0010 (Castro et al 2011)	Not a factual error. In the ERG Report we explicitly refer to the company submission (CS), ITC Report, and SLR report as three separate documents. This is important for clearly signposting the sources of information. The CS does not report any demographic details or quality assessment for trial Res-5-0010 and does not mention that the ITC report contains any information about this trial.
Page 20 "The company (despite a request for clarification from the ERG via NICE) is unclear about the relevance of the trial Res-5-0010: this trial was identified in the systematic review, then excluded by the company, then subsequently included in some outcome analyses."	Amend statement to: The reslizumab trial Res-5-0010 was included in the SLR, as well as in the direct comparisons and ITC when it reported on outcomes of interest.	Table 5 of the ITC Report clearly states that Res-5-0010 is to be considered for the meta-analyses and ITC. Some of the confusion around this trial's inclusion may be due to an omission/typo in Table 8 of the ITC report, where Castro et al. 2011 (Res-05-0010) appears to be missing. It is however not missing from the subsequent table (Table 9) where a list of studies included in the meta-analysis of each endpoint assessed at both time	Not a factual error. The company identified trial Res-5-0010 in the SLR but according to both CS Table 12 and the company's response to ERG clarification question A9 the trial was excluded "because it was a small phase II proof of concept trial…". Despite this explicit exclusion, the trial was included in a number of outcome analyses. It is important that this inconsistent application of eligibility criteria is highlighted by the ERG as it risks introducing

		points of interest is provided. Moreover, Castro 2011 (Res-05-0010) appears in Tables 10, 14, 20, 22, 25, 29 of the ITC Report. This demonstrates that Res-5-0010 was included in the meta-analyses conducted. Tables 33 and 34 in the ITC Report provide the correct list of included trials in the ITC, per endpoint and time of assessment. These tables demonstrate that Res-05-0010 is included in the ITC analyses when it endpoint data is available. Tables 35, 40, 43, 48, 51, 55, 61, 62, 65, 68, 71, and 74 of the ITC report describe why each study was excluded for each of the endpoints assessed for the ITC.	selection bias as well as uncertainty.
Page 109 "The ITC Report presents the changes from baseline in each arm of four of the trials (excluding Res-5-0010) (ITC Report Figure 10, not reproduced here)," Page 114 "For the AQLQ outcome assessed at 16±4 weeks the trial Res-5-0010 is included in the ITC of reslizumab versus omalizumab but excluded from	For the analysis of the AQLQ outcome at 16±4 weeks, Res-5-0010 is excluded from both the ITC and direct comparison of reslizumab versus placebo. Res-5-0010 should be removed from the reslizumab trials cell in "Table 61 Trials included in the ITC for AQLQ score change at 16±4 weeks".	The confusion around the inclusion/exclusion of Res-5-0010 for the analysis of this endpoint is due to a typo in the ITC Report; the row corresponding to this trial (Castro et al. 2011) in Table 48 of the ITC Report should state that this trial was excluded, with the reason for exclusion being 'No AQLQ data reported'. Table 48 will then be in line with Figure 10 of the ITC report which accurately presents the data used	This is a company error in Table 48 of the ITC Report, not an ERG factual error. However, since this is referred to in 5 places in the ERG report (pages 21, 108, 109, 113, 171) we have amended text on these pages for clarity.

the direct comparison of reslizumab versus placebo, without any explanation.”		in the analysis of AQLQ at 16±4 weeks. This amendment will allow to correctly describe the inputs used for the analysis and will not impact the relative treatment effect estimates obtained.	

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 11 (first instance) and throughout. The ERG report only considers trials 3082 and 3083 to be pivotal trials.	Where reference to pivotal trials are made, trial 3081 should be included.	There are three pivotal trials referred to in the CS (for example in section 4.3.1 of CS).	Not a factual error. The CS mentions that trials 3082 and 3083 are the pivotal trials (CS Table 1) and later mentions that trials 3082, 3083 and 3081 are the pivotal studies or pivotal trials (CS Table 12 and section 4.3.1). However, we have clarified that it is the ERG report which refers to trials 3082 and 3083 as the pivotal trials (page 11).

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 12 (first instance) and	Change 16±1 to 16±4 throughout the	The 16±1 follow-up point is	Not a factual error. The ERG

throughout. The ERG report frequently uses 16±1 as a follow-up data point when reporting results from the direct treatment comparison.	report.	inaccurate. The correct follow-up point used in the direct treatment comparison was 16±4.	Report specifies the exact time points employed in the analyses, as explained on ERG Report page 62 (direct comparisons) and page 67 (indirect comparisons).

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 13 The ERG report states: "For discontinuations due to adverse events (3 trials) the fixed and random effects models gave identical results, which showed no statistically significant differences between reslizumab and placebo treated patients at either 16±1 weeks (odds ratio 0.83; 95% CI 0.17 to 4.16) or 52 weeks (odds ratio 0.70; 95% CI 0.33 to 1.5)."	The statement should be amended to include the number trials (n=2) used to inform the result for 52 weeks.	The current statement is inaccurate. While three trials were included in the analysis at 16±4 weeks, only two trials reported data at 52 weeks.	We agree and we have added text to clarify that 2 trials were included in the 52 weeks comparison of discontinuations due to adverse events (pages 13 & 89).

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 13	This statement should be expanded to include the results from the analysis of	This statement is incorrect as data from three trials were available for	We agree and we have added the missing text for SAEs at 16±1

With regards to serious adverse events (SAE), the ERG report states: For serious adverse events up to 52 weeks (2 trials) the fixed and random effects models gave identical results, and these showed no statistically significant differences between the reslizumab and placebo groups (odds ratio 0.71; 95% CI 0.47 to 1.08). Insufficient data were available for analysis at 16 weeks.	SAEs at 16±4 weeks: For serious adverse events, the fixed and random effects models gave identical results, and these showed no statistically significant differences between the reslizumab and placebo groups at 16±4 weeks (3 trials; odds ratio 0.82; 95% CI 0.43 to 1.55) and at 52 weeks (2 trials; odds ratio 0.71; 95% CI 0.47 to 1.08).	SAEs at 16 weeks in the CS (page 148).	weeks as suggested. This applies on ERG report pages 13, 89, 90 & 91.

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Results of the random effects model not being presented. Page 15 "however, the robustness of these results is unclear given that no random-effects analysis is available for comparison." Page 21 "The CS selectively presents only fixed-effects model results for the analysis of clinically significant exacerbation rates when a random-effects analysis should at least have	The ITC Report presents results of the fixed effects model in the base case analysis of clinically significant exacerbation. This choice was purely based on the DIC. Results of the random effects model are presented in Appendix 12 of the ITC Report.	It is inaccurate to suggest that no random-effects analysis was available. The ITC report presented the random-effects analysis in appendix 12 to allow the evaluator to compare the impact of model selection on the analytical outputs and interpretation of ITC results.	We agree (the random effects results were inadvertently missed by us as they are in a separate appendix, not given alongside the fixed effects results and not discussed by the company). This is mentioned on 6 pages of the ERG report and we have updated the text on these (pages 15, 21, 100, 101, 114, 171).

been presented for comparison.”			

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 19 (first instance) Several statements in the ERG report include values/figures that should be commercial in confidence (CIC).	Highlight as CIC. i. **Page 19**: “The probabilistic sensitivity analysis (PSA) estimated a [redacted] and [redacted] probability that reslizumab is cost effective at a willingness to pay threshold of £20,000 and £30,000 per QALY gained, respectively.” ii. **Page 161**: “at a threshold willingness to pay of £20,000 and £30,000 per QALY gained (in the revised model), that there is a [redacted] and [redacted] probability of reslizumab being cost-effective respectively.” iii. **Table 94:** Mean ICERs to be highlighted: £23,940 [redacted] iv. **Page 165: “**At thresholds for willingness to pay of £20,000 and £30,000 per QALY gained, that there is a [redacted] and [redacted] probability of reslizumab being	The current statements are CIC as in CS and appendix 4 of the company response.	i – vii: The CIC data have been highlighted as suggested (pages 19, 159, 163, 164, 169, 172).

	cost-effective respectively." v. **Figure 11.** Figure to be marked as CIC vi. **Page 171: "**The company's PSA indicated that at a threshold of £20,000 per QALY there would be a [redacted] probability that reslizumab is cost-effective and at £30,000 per QALY this probability increases to [redacted]" vii. **Page 174: "**The company's probabilistic sensitivity analyses showed there is a probability of [redacted] and [redacted] that reslizumab is cost effective at a willingness to pay threshold of £20,000 and £30,000 respectively		

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 21 "The reported sample sizes for the reslizumab trials analysed in the ITC are different to those for the same trials when analysed for the same outcomes in the direct comparison; furthermore, for some outcomes sample sizes are markedly smaller than the number randomised and (where defined) smaller than the 'full	The reslizumab trial samples used in the ITC were the same as in the direct comparisons. These sample sizes correspond to the efficacy sample sizes extracted in each outcome's table in the efficacy sections of the CSR. The sample sizes displayed on the ITC Report figures presenting the ITC inputs are therefore not the correct inputs as they were not used in the statistical	The correct sample sizes used for reslizumab trials are those reported in the tables of inputs for the direct comparisons (Tables 10, 12, 14, 16, 18, 20, 22, 23, 25, 27, 29, and 31). These sample sizes were extracted from efficacy sections in the clinical study reports (CSR) and were associated with the treatment	These are company errors, not factual errors of the ERG. However, we have added a statement on ERG report pages 21 & 171 to clarify that the company provided further information about this after the ERG report submission.

analysis set'." 	analysis. The efficacy sample sizes reported in the CSR and used in both direct comparison and ITC analyses are smaller than the randomised population.	effects reported. These efficacy sample sizes reported in the CSR are indeed smaller than the number randomised. The N shown on the figures used to present the inputs for the ITC analyses are those of the randomised population. This can lead the evaluator to confusion as these were not used as sample size in the ITC analyses. ITC analyses were based on the same main data set as the direct comparison, meaning that the ITC used the same reslizumab trial sample sizes as that which was used in the direct comparisons.	

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 30 and Table 3 (page 31) The ERG report states that: "the solution being available in 100 mg/10 mL (10 mg/mL) single use vials."	Amend the current statement to include: A 25 mg vial is currently under development and expected to be available between [redacted].	The current statement omits the 25 mg vial in development. The 25 mg vial size will shortly be available, and the base case analysis was based on this option.	Not a factual error. The statements on page 30 and in ERG Table 3 are referring to the SmPC and CS Table 2. However, the future availability in 25 mg vials is relevant to the company's base case and this is explained in ERG Report section 4.3.4.

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 39 Typo in the following statement: "…phase II proof of concept study that informed the phase II clinical programme."	Amend statement to: "…phase II proof of concept study that informed the phase III clinical programme."	The current statement is inaccurate.	We agree. This correction has been made (page 40)

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 4 (page 42) i. Change from baseline in AQLQ and ASUI omitted from secondary/tertiary outcomes for Trial 3084 ii. For trial 3081, the exploratory variables are not clearly separated from the secondary/tertiary outcomes	i. Include AQLQ and ASUI in the list of secondary/tertiary outcomes for Trial 3084 ii. Clearly separate the exploratory variables from the secondary/tertiary outcomes for Trial 3081 using a new table cell (as for trials 3082 and 3083)	i. The current list is inaccurate ii. To help readers clearly interpret what the exploratory variables for Trial 3081 were	i. Not a factual error. The reason these outcomes are not included in ERG Table 4 is because they are not mentioned as secondary or tertiary outcomes in CS Tables 52 or 55. ii. We have updated the table cells as requested (pages 42-43); however, this seems largely academic as no explanation is given in the CS as to how outcomes classified as secondary, tertiary or exploratory differ.

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 43 The ERG report states: "For trial 3084 the CS describes the patient characteristics as well balanced (CS Table 53), except that the proportion of females in the reslizumab arm (66%) was slightly higher than in the placebo arm (55%)."	Amend the statement to: "For trial 3084 the CS describes the patient characteristics as well balanced (CS Table 53), while highlighting that the proportion of females in the reslizumab arm (66%) was slightly higher than in the placebo arm (55%)."	The current statement could be interpreted as the CS failed to observe the imbalance in the proportion of female patients in each treatment arm.	We agree and have made the suggested amendment (page 44).

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 5 (page 48) For Trial 3084, patients with exacerbations in last 12 months is reported as 'NR'.	Amend the table to include the following values: RES: 166 (42) Placebo: 37 (38)	The current use of NR in the table is inaccurate as data for patients with exacerbations in last 12 months in Trial 3084 was reported in Table 53 of the CS.	We agree and have made the suggested amendment (page 49).

Issue 14

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 53 "As shown in Table 6, we concur with the company's judgement provided in the CS version."	Amend statement to: "As shown in Table 6, we concur with the company's judgement provided in the ITC report."	The current statement is inaccurate.	We agree and have made the suggested amendment (page 54).

Issue 15

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 7 (page 58) The table contains inaccuracies in the presented data.	i. 3082, Placebo, 4th column (from the left): 243 (97%) should be 244 (100%) ii. 3084, Reslizumab, 4th column: 395 (99%) should be 395 (>99%) iii. 3084, Both arms, 5th column: The values to be added are: RES: 395 (>99%) Placebo: 97 (99%)	The current table is inaccurate. i. As in CONSORT diagram (Figure 2, page 65 of CS) ii. As in CONSORT diagram (Figure 35, page 127 of CS) iii. As in the CONSORT diagram (Figure 35, page 127 of CS)	i. Not a factual error. The numbers given here by the company do not agree with the text immediately above Figure 2 in the CS which states 488 patients were in the FAS (the company's numbers would give 489 in the FAS). ii. Not a factual error. Percentages in the table are consistently rounded to the nearest integer, except for values of ≥99.5% which, being near-ceiling values, are reported as ">99%" iii. The missing values (rounded, as mentioned above) have been added to Table 7 as requested (page 59).

Issue 16

<table>
<tr><th>Description of problem</th><th colspan="3">Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr><td rowspan="6">Incorrect section/page/table numbers in the CS cited.</td><td>ERG page number</td><td>Citation</td><td>Correction</td><td rowspan="6">Cited section/page/table numbers in the CS are inaccurate.</td><td rowspan="6">These cross-references have been corrected (pages 62, 82, 153, 163).</td></tr>
<tr><td>61</td><td>(CS page 49)</td><td>(CS Section 4.9)
or
(CS page 135)</td></tr>
<tr><td>Table 24</td><td>Source: CS Tables 58 & 59</td><td>Source: CS Tables 58 & 60</td></tr>
<tr><td>Table 88</td><td>(CS Table 117, p205)</td><td>(CS Table 117, p206)</td></tr>
<tr><td>165</td><td>CS Tables 131 and 131</td><td>CS Tables 131 and 132</td></tr>
</table>

Issue 17

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 84 The ERG report states: “Adverse events in all categories (mild, moderate, severe) occurred in both the reslizumab and placebo groups, with a tendency for most categories to be slightly	Suggested amendment The claim that most categories were slightly more frequent in the reslizumab group should be revised to Overall, the incidence of any AE	The claim that most categories were slightly more frequent in the reslizumab group is inaccurate: i. Overall, the incidence of any AE was more frequent in the placebo	We agree. The ERG statement on page 85 should have read “placebo” rather than “reslizumab” and the intention was to give a general overview of AEs. However, as the company’s suggested text is more precise

more frequent in the reslizumab group.”	was more frequent in the placebo arm. While mild AEs were more frequent in the reslizumab arm (3/3 trials reporting mild AEs), moderate AEs were more frequent in the placebo arm (3/3 trials reporting moderate AEs). SAEs were more frequent in the placebo arm in 2/4 trials reporting SAEs. Across the four trials, the average % incidence of SAEs was 7.25% in reslizumab-treated patients and 8.5% in placebo-treated patients.	arm ii. While mild AEs were more frequent in the reslizumab arm (3/3 trials reporting mild AEs), moderate AEs were more frequent in the placebo arm (3/3 trials reporting moderate AEs) iii. SAEs were more frequent in the placebo arm in 2/4 trials reporting SAEs. Across the four trials, the average % incidence of SAEs was 7.25% in reslizumab-treated patients and 8.5% in placebo-treated patients	and we agree that it is accurate, we have added this whilst making the correction.

Issue 18

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 31 (page 87) Incorrect patient number in reslizumab arm of Trial 3081.	Change N=571 to N=103	Current value is inaccurate.	We agree and have corrected the number (page 88).

Issue 19

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 88 and Table 32 (page 88) Data for discontinuations due to adverse events incorrectly attributed to trials 3081 and 3084.	i. Change: "…events at 16±1 weeks and two (3081 and 3084) to data at 52 weeks" To "…events at 16±4 weeks and two (3082 and 3083) to data at 52 weeks" ii. Amend table 32 to include rows for 3082 and 3083 and add 52-week data to these rows	The current statement and table is inaccurate as 52-week data for discontinuations due to adverse events were derived from trials 3082 and 3083	This is covered by our response to Issue 5.

Issue 20

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 40 (page 94) Missing indication that presented values in columns 2–4 are LS mean values.	State that the values in the table are LS mean values (as in Table 41 of the ERG report).	The values are not mean values but LS mean values.	We have added text to clarify that the data are LS means. For trial 3084 we have changed the reported value (standard mean) to LS mean for consistency (page 94).

Issue 21

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 95 The ERG report states: "The decline in ACQ score was significantly larger with reslizumab than with placebo in the ≥400 eosinophils per µL subgroup"	Change statement to: "The decline in ACQ score was numerically larger with reslizumab than with placebo in the ≥400 eosinophils per µL subgroup"	The current statement is inaccurate as the decline in ACQ score was not significantly different (p=0.0643) with reslizumab than with placebo in the ≥400 eosinophils per µL subgroup.	We have amended the text to clarify that the only statistically significant difference between groups was in the full trial population (pages 95-96).

Issue 22

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 118 The number of references excluded is stated as 2,661.	Change 2,661 to 2,660	The current statement is inaccurate. 2681 publications were screened and 21 publications were included (2660 excluded)	We agree. We have changed the number of references to 2,660, as suggested (page 117).

Issue 23

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 132, 133, and 134 The ERG report states that the reslizumab transition probabilities for the three time	In response to the clarification question requesting the full calculations necessary for determining transition probabilities	The transition probabilities reported in the excel model, in the "Transition_matrices_RES" worksheet are the same as the	We agree and have amended the text on pages 131, 132 & 134 to clarify that the transition probabilities for the reslizumab

periods used in the model differ from those calculated using data from studies 3082 and 3083. In particular, on pages 134/135: "The transition probabilities used in the model (Table 75) are not identical to the probabilities reported from the individual patient data (Table 76) and the ERG could not check the validity of the company estimates or replicate their calculations".	and the assumptions for these calculations, the company provided the transition probability calculations derived from the 3082 and 3083 studies for the reslizumab arm. However, the calculations detailed within the model to derive the transition probabilities adjusted for the increased exacerbation rates, done in the "Clinical_parameters" spreadsheet of the model were not further described in the response."	probabilities reported in the supplementary confidential workbook. These reflect the transitions observed in the studies 3082 and 3083. However, the probabilities displayed in the "Clinical_parameters" worksheet of the excel model are further adjusted to reflect the increased rate of exacerbations. The CS reported on page 189 that these were indeed the adjusted transition probabilities: "*In order to maintain the relative treatment effect of reslizumab, the multiplier applied to BSC to match the annual rate of response in the year preceding enrolment in the clinical trial was applied to all transition probabilities of moving to the exacerbation health states. The results are presented in Table 106".*	arm estimated directly from the studies 3082 and 3083 were adjusted using the multiplier. We have also removed references to our inability to replicate the company calculations on pages 138 and 172.

Issue 24

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 94 (page 165) Base case mean ICER for reslizumab vs omalizumab.	Change £12,889 to <u>£12,888</u>	Mean ICER is £12,888 in appendix 4 of the company response.	We agree. We have changed the value to £12,888 as suggested (page 163).

Issue 25

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 169/170 The ERG report states that after adjusting the monitoring time for the omalizumab regimen from 30 minutes to 15 minutes the total cost of omalizumab decreased from [redacted]	Repeat the calculations and update Table 100. TOTAL COSTS: BSC = [redacted] Omalizumab = [redacted] **(ERG reported, [redacted])** Reslizumab = [redacted] TOTAL QALYs: BSC = [redacted] Omalizumab = [redacted] Reslizumab = [redacted] Incremental ICER Omalizumab vs. BSC = £36,617 Omalizumab is extendedly dominated by reslizumab **(ERG reported, £23,302)** Reslizumab vs. BSC = £24,907 **(ERG reported, £26,390 vs omalizumab)**	We assumed the 15 minute monitoring time, by changing cell H43 of the "Costs_background" sheet in the model using the following formula =(£59/60)*(10+15), to account for the 10 minutes preparation time, that is not discussed in the ERG report and the 15 minute administration time. We obtained the following result for Omalizumab, total costs for omalizumab: [redacted], ICER vs BSC = £36,617, Omalizumab is extendedly dominated by reslizumab. The model produces an ICER of £14,090 for reslizumab vs omalizumab in this scenario. We question how the revised assumption could lead to an ICER of £23,302, as assumption no monitoring and preparation time for omalizumab (administration costs=£0) leads to an ICER for omalizumab vs BSC of £34,449 (omalizumab is extendedly dominated by reslizumab).	We agree. These are typographic errors and should be as suggested by the company. We have changed the cost for omalizumab to £114,895 and the ICER to omalizumab is extendedly dominated by resilizumab (pages 167, 168).