

Reslizumab for Treating Asthma with Elevated Blood Eosinophils Inadequately Controlled by Inhaled Corticosteroids: An Evidence Review Group Perspective of a NICE Single Technology Appraisal

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Abstract As part of the National Institute for Health and Care Excellence (NICE) Single Technology Appraisal (STA) process, the manufacturer of reslizumab (Teva) submitted evidence for its clinical and cost effectiveness for the treatment of eosinophilic asthma inadequately controlled by inhaled corticosteroids. NICE commissioned Southampton Health Technology Assessments Centre (SHTAC) as an independent Evidence Review Group (ERG) to provide a critique of the manufacturer's submitted evidence. Reslizumab is compared with best standard of care and omalizumab, for a small 'overlap' population of patients who have both eosinophilic and IgE-mediated severe asthma. This paper provides a summary of the ERG's review of the manufacturer's submission, and summarises the NICE Appraisal Committee's subsequent guidance (issued in August 2017). The ERG considered that there were limitations in the approach proposed by the manufacturer for the exacerbation rate and the utility for severe exacerbation. The company amended their initial analysis, following comments from the ERG and the NICE committee, whereby the incremental cost effectiveness ratio was £29,870 per QALY gained for reslizumab compared with best standard care. The NICE Appraisal Committee (AC) concluded that reslizumab was recommended as an option for the treatment of severe eosinophilic asthma that is inadequately controlled in adults despite maintenance therapy with high-dose inhaled corticosteroids plus

another drug, only if (1) the blood eosinophil count has been recorded as 400 cells per microlitre or more and (2) the patient has had three or more asthma exacerbations in the past 12 months, and (3) the company provides reslizumab with the discount agreed in the patient access scheme.

Key Points for Decision Makers

Reslizumab is a well tolerated and effective treatment in reducing the rate of clinically significant exacerbations for eosinophilic asthma that is inadequately controlled by inhaled corticosteroids.

There is no head-to-head trial evidence comparing reslizumab with omalizumab and there was considerable uncertainty in the comparison of these treatments.

The National Institute for Health and Care Excellence concluded that reslizumab would be a cost-effective use of the National Health Service resources and recommended its use in patients with eosinophilic asthma who have three or more exacerbations per year.

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1 Introduction

The National Institute for Health and Care Excellence (NICE) is an independent organisation responsible for providing national guidance for a number of areas for the

National Health Service (NHS). NICE assesses the clinical and cost effectiveness of new health technologies in order to provide recommendations for their use within the NHS.

The NICE single technology appraisal (STA) process usually evaluates a single health technology for a single indication, as near to its UK market authorisation as possible. The clinical effectiveness and cost-effectiveness evidence required for an STA is supplied by the manufacturer of the technology in the form of a manufacturer submission based upon a template and process developed by NICE. A report critiquing the manufacturer's evidence is then produced by an independent academic assessment unit appointed by NICE, referred to as the evidence review group (ERG).

The NICE Appraisal Committee evaluates the evidence provided by a number of stakeholders in order to reach conclusions on the clinical and cost effectiveness of the new technology and decides whether the technology is an appropriate use of NHS resources. The stakeholders providing evidence to the NICE committee include the ERG, clinical experts and patients or their representatives. Following the appraisal committee meeting, the NICE committee formulates preliminary guidance, which is referred to as the Appraisal Consultation Document (ACD). After stakeholders have submitted their comments on the ACD, the NICE committee issues final guidance, referred to as a Final Appraisal Determination (FAD).

This article presents a summary of the ERG's review and critique of the manufacturer's submission for the STA of reslizumab for treating asthma in patients with elevated blood eosinophils inadequately controlled by inhaled corticosteroids (ICS), and a summary of the subsequent development of the NICE guidance [1]. The appraisal documents, including the manufacturer's evidence submission, the ERG report, and the NICE appraisal committee decision documents are available on NICE's website [2].

2 The Decision 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) [3]. Asthma was responsible for 1216 deaths in 2014 [3]. Asthma costs the NHS an estimated £1 billion a year (2010–11 data), with the cost burden being driven by severe cases [4].

Asthma is characterised by variable and recurring symptoms. An asthma 'exacerbation' or 'attack' refers to a worsening of 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 their work, exercise, travel and leisure, as well as reducing their sense of wellbeing due to fear of having further symptoms or exacerbations [5].

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) [6]. The BTS/SIGN treatment approach is very similar to the stepwise approach recommended by the Global Initiative for Asthma (GINA) [7]. 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. 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 [8]. Patients who have asthma with elevated blood eosinophils inadequately controlled by ICS are classified as having severe asthma, managed according to Step 4 or Step 5 of the BTS/SIGN and GINA treatment pathways. The current guidelines indicate that people having high-dose therapies, or continuous or frequent use of oral steroids, should be referred for specialist care. For the majority of patients whose asthma is not controlled at Steps 4 and 5, the treatment options are limited and consist currently of further increasing the dose of 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 [6] and diminished corticosteroid sensitivity [9]. Best standard of care (BSC) is high dose ICS in combination with other controlled medications, with or without OCS. BSC relies on the use of a Personal Asthma Action Plan, the avoidance of environmental and dietary triggers and the use of recommended medications.

Despite best therapeutic attempts, for a small subgroup of around 5–10% of patients with eosinophilic asthma, the disease remains inadequately controlled at Steps 4 and 5. A small proportion of these patients who also have severe persistent IgE-mediated asthma may be eligible for treatment with omalizumab.

Reslizumab (Teva), is a monoclonal anti-IL-5 antibody used in addition to BSC and 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. Relevant comparisons for

this technology appraisal are reslizumab versus BSC and, for a small ‘overlap’ population of patients who have both eosinophilic and IgE-mediated severe asthma, reslizumab versus omalizumab.

Reslizumab is administered intravenously at a recommended dose based on patient weight of 3.0 mg/kg and given once every 4 weeks. Omalizumab is a monoclonal antibody that binds to IgE. It 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 (Investigation of Omalizumab in Severe Asthma Treatment) trial to estimate the average dose and the number of omalizumab treatments that occur in 28 days [10]. Both reslizumab and omalizumab are provided with patient access schemes (PAS), which are confidential price discounts to the NHS.

The anti-IL-5 monoclonal antibody mepolizumab is also licensed as an add-on treatment for severe refractory eosinophilic asthma in adults. Mepolizumab had not yet been appraised by NICE at the time of the single technology assessment for reslizumab and was not included by NICE as a comparator in the reslizumab appraisal.

The NICE scope for this technology appraisal compares the clinical and cost effectiveness of reslizumab with BSC and omalizumab for adults with asthma with elevated blood eosinophils inadequately controlled with ICS.

3 The Independent Evidence Review Group (ERG) Review

3.1 Clinical Evidence Provided by the Manufacturer

The manufacturer’s evidence consisted of five randomised controlled trials (RCTs) that directly compared reslizumab with placebo (Table 1). No direct comparisons of reslizumab and omalizumab were available. The manufacturer identified 16 RCTs that compared omalizumab with placebo, BSC or ‘optimised asthma therapy’ to support an indirect treatment comparison (ITC) between reslizumab and omalizumab. An implicit assumption was that placebo and optimised asthma therapy arms in these trials were equivalent to BSC, and therefore could be used as a common comparator in the ITC.

In each of the five reslizumab RCTs, the intervention group received reslizumab 3.0 mg/kg administered every 4 weeks in accordance with the Summary of Product Characteristics. The reslizumab trials were all double-blind and all were sponsored by the manufacturer or by one of its subsidiaries (Res-5-0010). The manufacturer’s key direct evidence for the reslizumab–placebo comparison is

primarily taken from two of the five RCTs, trials 3082 and 3083 [11], which we refer to as the pivotal reslizumab trials. These had a 52-week duration and identical designs, with clinically significant exacerbation rates (called ‘clinical asthma exacerbation rates’) as their primary outcome. The remaining reslizumab trials (3081, 3084 and Res-5-0010) had durations of 15 or 16 weeks, with lung function and asthma control as their primary outcomes (Table 1). They differed slightly in their inclusion criteria compared with the pivotal trials; in particular, trial 3084 did not require patients to have ≥ 400 eosinophils per microlitre at baseline so the inclusion criteria for this trial does not align with the marketing authorisation for reslizumab.

3.1.1 Direct Comparison Between Reslizumab and Placebo

The manufacturer conducted direct meta-analyses comparing reslizumab with placebo for several outcomes, including rates of clinical asthma exacerbations standardised to person-years, hospitalisations due to exacerbations, serious adverse events, discontinuations due to adverse events, changes in asthma control questionnaire (ACQ) scores, changes in lung function, and changes in HRQoL scores from the Asthma Quality of Life Questionnaire (AQLQ). These outcomes were consistent with the NICE scope. A frequentist method was used for the meta-analyses except for the exacerbation rates, which were analysed using a Bayesian approach (the ERG considered this to be appropriate, given the different formats of the outcomes). Fixed-effects and random-effects analyses gave nearly identical results for all outcomes except exacerbation rates, and the random-effects results are shown in Table 2. The rate of clinical asthma exacerbations was statistically significantly lower in the reslizumab group than the placebo group with a fixed-effects model [hazard ratio 0.44; 95% credible interval (CI) 0.35–0.56], but did not differ significantly with a random-effects model (hazard ratio 0.43; 95% CI 0.17–1.10). The only clinical effectiveness outcome that directly informed the manufacturer’s economic analysis was the standardised rate of asthma exacerbations. The manufacturer provided a meta-analysis of trials 3082, 3083 and Res-05-010 for this outcome (Table 2), but the exacerbation rates in the manufacturer’s economic model were based on individual patient data from trials 3082 and 3083 rather than from the meta-analysis hazard ratio.

3.1.2 Indirect Treatment Comparison Between Reslizumab and Omalizumab

The ITC assumed that effects of omalizumab are comparable in patients irrespective of their blood eosinophil levels. This assumption was necessary because only

Table 1 Randomised controlled trials comparing reslizumab (3.0 mg/kg body weight every 4 weeks) with placebo

Trial name/number	Location	Number randomised	Duration	Baseline blood eosinophils/ μL	Primary outcome
Manufacturer trial 3082 [11]	102 centres in 17 countries	489 (2 arms)	52 weeks	Mean $\geq 400^b$	Clinical asthma exacerbation frequency
Manufacturer trial 3083 [11]	82 centres in 15 countries	464 (2 arms)	52 weeks	Mean $\geq 400^b$	
Manufacturer trial 3081 [12]	68 centres in 12 countries	315 (3 arms ^a)	16 weeks	Mean $\geq 400^b$	Lung function (FEV_1 change)
Manufacturer trial 3084 [13]	103 centres in the US	496 (2 arms)	16 weeks	Mean 280 ^b	
Res-5-0010 [14]	25 centres in the US and Canada	106 (2 arms)	15 weeks	Median 500 (range 0–1500)	Asthma control (ACQ score change)

ACQ Asthma Control Questionnaire, FEV_1 forced expiratory volume in one second

^aTrial included a 0.3-mg/kg reslizumab arm (outside the licence and not assessed)

^bInclusion criteria specified baseline blood eosinophils $\geq 400/\mu\text{L}$

^c $\geq 400/\mu\text{L}$ and $< 400/\mu\text{L}$ subgroups reported for some outcomes

Table 2 Direct meta-analysis results: reslizumab versus placebo

Outcome	Timing (weeks)	Random effects estimate (95% CI)	Trials included	Key uncertainties
ACQ score change, mean difference	16	−0.24 (−0.32 to −0.17)	All 5 RCTs ^a	Unexplained missing data (<2–20% per trial)
Clinical asthma exacerbations/ person-years, hazard ratio	52	Median 0.43 (credible interval 0.17 to 1.10)	3082, 3083, Res-5-0010	Unexplained missing data (0.8–2.1% per trial)
FEV_1 change (L), mean difference	16	0.13 (0.07 to 0.18)	All 5 RCTs ^a	Unexplained missing data (1.9–20% per trial)
	52	0.13 (0.08 to 0.18)	3082, 3083	Unexplained missing data (0.8–2.1% per trial)
Serious adverse events, odds ratio	52	0.71 (0.47 to 1.08)	3082, 3083	Sample size slightly smaller than reported safety set
Discontinuation due to adverse events, odds ratio	16	0.83 (0.17 to 4.16)	3081, 3084, Res-5-0010	
	52	0.70 (0.33 to 1.5)	3081, 3084	
AQLQ score change, mean difference	16	0.24 (0.12 to 0.36)	3082, 3083, 3081	Inconsistent sample sizes reported; unexplained missing data
	52	0.33 (0.19 to 0.46)	3082, 3083	

ACQ Asthma Control Questionnaire, FEV_1 forced expiratory volume in one second, AQLQ Asthma Quality of Life Questionnaire, RCTs randomised controlled trials

^aIncluded patients from trial 3084 with baseline blood eosinophils $< 400/\mu\text{L}$

patients in the reslizumab trials had elevated blood eosinophil levels (only one of the omalizumab trials [15] included any patients with both IgE-mediated and eosinophilic asthma in a subgroup that had baseline blood eosinophils $\geq 260/\mu\text{L}$, i.e. lower than in the reslizumab trials; the company did not include this subgroup in the ITC).

The ITC was based on a simple network, comprising only trials of reslizumab versus placebo and trials of omalizumab versus placebo, BSC, or optimised asthma

care. The statistical method for the ITC of clinical exacerbation rates used a Bayesian approach, which the ERG considered to be appropriate.

ITC results for rates of clinical asthma exacerbations, standardised to person-years, are based on three reslizumab and three omalizumab trials. The fixed-effects ITC hazard ratio favoured reslizumab over omalizumab in terms of having a lower standardised rate of clinical asthma

exacerbations (0.80; 95% CI 0.44–1.44). Results for random-effects ITC were not reported.

3.1.3 ERG's Critique of the Clinical Evidence and Interpretation

The manufacturer's systematic review identified all relevant evidence for reslizumab and the majority of evidence for omalizumab (which was identified to inform the ITC). The included trials of reslizumab were of generally good quality. The main limitation of the clinical trials is that their duration (15–52 weeks) is relatively short given that asthma is a chronic condition.

There were inconsistencies in the sample sizes reported for the direct comparison meta-analyses (Table 2); however, these data were not used in the economic analysis and so do not influence the cost-effectiveness conclusions.

The manufacturer's process for selecting trials for the ITC based on their definitions of clinical asthma exacerbations was inconsistent, meaning that several omalizumab trials may have been unnecessarily excluded from analysis. The manufacturer submission presented only fixed-effects model results for the analysis of clinical asthma exacerbation rates when a random-effects analysis should at least have been presented for comparison. Some of the reported sample sizes for the reslizumab trials analysed in the ITC were different to those for the same trials when analysed for the same outcomes in the direct comparison; and, for some outcomes, sample sizes were markedly smaller than the number randomised. The manufacturer also failed to indicate that not all omalizumab trials had a placebo or BSC comparator and it was unclear whether 'optimised asthma control' or 'control group' arms in omalizumab trials are equivalent to BSC. The ERG concluded that the ITC results could be at high risk of bias, as the methods of analysis appeared inconsistent and not transparent, and were inadequate to protect against systematic errors.

3.2 Cost-Effectiveness Evidence Provided by the Manufacturer

The manufacturer's de novo cost-effectiveness analysis used a Markov model to estimate the cost effectiveness of reslizumab compared with BSC and omalizumab. The model adopted a time horizon of 60 years and a cycle length of 4 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 1 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 UK NHS and Personal Social Services.

The pivotal trials recruited patients with one or more exacerbations in the year preceding randomisation. The manufacturer concluded that a more restricted population with more than three exacerbations in the year before randomisation would be more suited to clinical use in the NHS and used this population for their submission. Table 3 shows the mean annual rates of exacerbations for the year prior to randomisation and for the year after randomisation in the placebo arms of trials 3082 and 3083. The first row presents the overall rates for all adult patients at GINA steps 4 and 5 and the other rows show subgroup analyses according to the number of exacerbations in the preceding year. Trial patients in both the reslizumab and placebo arms had reductions in their exacerbation rates in the year after randomisation when compared with the year preceding randomisation.

The manufacturer's analysis was for a cohort of patients who had experienced at least three exacerbations in the year preceding the clinical trial. 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 population used to estimate the transition probabilities was a subgroup of the patients at step 4 or 5 in the GINA pathway who had experienced at least two exacerbations in the preceding year, rather than the company's target population for the base-case model of at least three exacerbations. This was justified by the manufacturer on the basis of a small sample size ($n = 91$) in the latter group.

The manufacturer adjusted the exacerbation probabilities using an exacerbation multiplier to inflate the rate of exacerbations experienced in the BSC and reslizumab arms so that the exacerbation rate in the BSC arm was the same as observed in the year before randomisation. The company stated they applied this adjustment in order to reflect the rates of exacerbation expected to be observed in clinical practice. For the omalizumab treatment arm, rates of exacerbation after 16 weeks were based on an analysis for responders in the INNOVATE trial [10]. Rates of asthma control and response to treatment for omalizumab were assumed equal to those for reslizumab.

The manufacturer conducted a systematic review for costs and HRQoL. The manufacturer used HRQoL data from studies by Willson et al. [16] and Lloyd et al. [17]. These studies, involving patients with asthma at GINA

Table 3 Mean annual rates of exacerbations in placebo arms (studies 3082 and 3083)

Subpopulation	N ^a	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	307	3.37	2.13	1.59
Adults; GINA Step 4 and 5, ≥ 3 exacerbations in the preceding year	158	4.67	2.73	2.15
Adults; GINA Step 4 and 5, ≥ 4 exacerbations in the preceding year	94	5.81	2.88	2.62

GINA Global Initiative for Asthma

^aERG note: the numbers of patients (*N*) in this table (from the manufacturer submission) do not match the numbers of patients in the placebo arms of studies 3082 and 3083 (*n* = 476)

steps 4 and 5, reported EQ-5D data using the UK tariff and were used to provide health state utility values in the model for patients with severe asthma. The health state utility values were 0.92 for controlled asthma, 0.728 for uncontrolled asthma, 0.57 for moderate exacerbation and 0.33 for severe exacerbation. The model contained resource use and cost data for drugs (including administration), nurse and general practitioner visits, specialist visits, emergency medicine and hospitalisation. The costs were valued in the year 2016.

Results of the economic model were presented as the incremental cost per quality-adjusted life-year (QALY) and included the PAS for reslizumab. The patient population eligible for treatment differed between omalizumab and reslizumab and so the manufacturer presented separate analyses for reslizumab versus BSC, and for reslizumab versus omalizumab. The results of the base-case cost-effectiveness analyses showed an incremental cost-effectiveness ratio (ICER) of £24,907 per QALY gained for reslizumab compared with BSC and an ICER of £16,643 per QALY gained compared with omalizumab.

The manufacturer performed a range of deterministic and probabilistic sensitivity analyses to assess uncertainty. The ICER remained below £30,000 per QALY gained in all deterministic sensitivity analyses, with the exception of reducing the time horizon to 5 years. The analyses were most sensitive to the rate of exacerbations for the BSC arm. The manufacturer provided analyses for subgroups according to the number of exacerbations experienced in the previous year by calibrating the transition probabilities against the exacerbation health states using an ‘exacerbation multiplier’. The ICER varied between £33,774 per QALY gained for patients who had experienced two or more exacerbations in the preceding year and £20,006 per QALY gained for patients who had experienced four or more exacerbations.

The probabilistic sensitivity analysis (PSA) estimated a 28 and 69% probability that reslizumab is cost effective at a willingness-to-pay threshold of £20,000 and £30,000 per QALY gained, respectively.

3.2.1 Critique of the Cost-Effectiveness Evidence and Interpretation

The manufacturer applied an ‘exacerbation multiplier’, which inflated the rate of exacerbations. The reason that the manufacturer provided for the use of the multiplier was 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.

The ERG questioned the use of a multiplier to adjust the exacerbation probabilities in the BSC and reslizumab arms, as the base-case analysis should have reflected the observed levels of risk in the clinical trials. It was not clear why there was a large change in the exacerbation rate in the BSC arm. It may have resulted (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 higher rates of exacerbations than they would usually. In addition, expert clinicians at the appraisal committee meeting suggested that patients in both arms of the trials would be carefully followed and monitored during the trial, which may lead to some improvement in outcomes.

The ERG also had concerns over the lack of clarity over the calculations used to estimate the transition probabilities. The manufacturer’s estimates of transition probabilities for the BSC arm were based on the subgroup of patients experiencing two or more exacerbations instead of their target population for the base case model of three or more exacerbations. The manufacturer suggested that this was justified on the basis of a small sample size (*n* = 91) in the latter group. However, the ERG noted that the

manufacturer 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.

Another concern over the clinical effectiveness parameters arose 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 for up to 60 years' duration.

The ERG had concerns with the utility values used in the manufacturer's analysis and considered that the utility values used for severe exacerbation were incorrect. We noted that the utility value for severe exacerbations in the study by Lloyd et al. [17] was defined where all patients in this state were hospitalised. This was inconsistent with the definition for severe exacerbation in the manufacturer submission, where a proportion (23%) were hospitalised and the remainder were not hospitalised. The ERG also noted that the study by Lloyd et al. [17] was based on a small number of patients, suggesting that it would have been more appropriate to use HRQoL data from the 3082 and 3083 reslizumab trials to map from AQLQ to EQ-5D.

A further limitation of the submitted economic analysis was that there was no evidence available from the trials or other data sources on the likely effect of reslizumab on oral steroid use. Use of oral corticosteroids was 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.

3.3 Additional Work Undertaken by the ERG

The ERG applied a series of modifications to the manufacturer's base-case analysis to address the limitations described above. The ERG conducted an analysis changing the assumptions used for the exacerbation multiplier. Rather than using the exacerbation multiplier to inflate the probabilities of exacerbation, the ERG used the exacerbation rates observed in the 3082 and 3083 clinical trials without adjustment. This modification increased the ICER of reslizumab versus BSC to £50,878 per QALY gained.

We recalculated the utility value for the severe exacerbation health state by calculating a weighted average with those who were hospitalised assigned the severe exacerbation utility value and those who were not hospitalised assigned the moderate exacerbation utility value. The

model was run with this utility value for severe exacerbations. With this modification, the ICER of reslizumab was £29,720 per QALY gained.

We also noted some inconsistencies of the reporting of the health state costs and the monitoring times used for omalizumab. Changes to these had only a minor effect on model results. The combination of all the changes described resulted in an ICER of £57,356 per QALY gained for reslizumab compared with BSC, while omalizumab was extendedly dominated by BSC for all analyses.

3.4 Conclusions of the ERG Report

Compared with placebo, the clinical effectiveness evidence suggested reslizumab may have improved asthma control, as measured by the ACQ, in the short term (data were only available up to 16 weeks) and improved HRQoL, as measured by the AQLQ, up to 52 weeks. The impact of reslizumab on exacerbation rate was equivocal due to lack of significance in a random-effects analysis. There were no unexpected safety concerns. However, as noted above, there were numerous inconsistencies in the manufacturer's submission regarding the studies included in the analyses and missing data, making the submission difficult to follow and appraise. The asthma control and HRQoL outcomes from the 3082 and 3083 trials were not used by the manufacturer to inform their economic analysis, whilst clinical exacerbation rates in the economic analysis were modelled using individual patient data.

The comparison of reslizumab and omalizumab in the ITC suffered from several limitations, which render the ITC results unlikely to be reliable. Due to limited availability of studies, it was necessary to assume that effects of omalizumab are comparable in patients irrespective of their blood eosinophil levels, which seems unlikely to be plausible. The manufacturer's process for selecting trials based on their definitions of clinical asthma exacerbations appeared inconsistent, meaning that several omalizumab trials may have been unnecessarily excluded from the analysis. There was also lack of clarity around the rationale given for study inclusion; lack of explanation for missing data; and clinical exacerbation rate results were presented only for fixed-effects analysis, when a random-effects analysis should at least have been presented for comparison.

The manufacturer submission included evidence on the cost effectiveness of reslizumab compared with BSC and omalizumab for severe asthma. The model structure adopted for the economic evaluation was generally appropriate and consistent with the clinical disease pathway. The model used 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 two previous exacerbations instead of the subgroups of patients with more than three previous exacerbations. Further, the ERG questioned 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 manufacturer submission presented all results at the confidential PAS price for reslizumab. The model results suggested that reslizumab had a cost effectiveness versus BSC of £24,907 per QALY gained.

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 manufacturer submission rather than the values used in the model. The ERG's alternative base-case analysis for reslizumab compared with BSC produced an ICER of £57,356 per QALY gained.

4 Key Methodological Issues

A key methodological issue for this appraisal was the approach taken regarding exacerbation rates used in the economic model. The manufacturer's 3082 and 3083 trials recruited patients with one or more exacerbations in the year preceding randomisation. A restricted population was used for the base-case analysis of patients who had three or more exacerbations in the preceding year. In the trial, patients in placebo and reslizumab arms both had a reduction in exacerbations. The manufacturer stated that this was a placebo effect and therefore applied a multiplier to the exacerbation transition probabilities. As stated previously, the manufacturer adjusted both the placebo and reslizumab arm using an exacerbation multiplier. The use of this exacerbation had a large (and favourable) effect on the cost effectiveness of reslizumab. The reduction in the exacerbation rates in the trial for the placebo arm may have been due in part to patients being followed more carefully and receiving optimised care, which they may not have received before entering the trial. In the ERG's view, the manufacturer should have used the trial data unadjusted in their base-case analysis and conducted sensitivity analyses with variations in the background exacerbation rate.

In this technology appraisal, reslizumab was compared with BSC. At the time, there was also a separate, concurrent NICE appraisal for mepolizumab for a similar population. Subsequently, mepolizumab was approved by NICE for this population [18]. Two issues arise from this: firstly, as mepolizumab and reslizumab have been appraised in separate technology appraisals, there is no comparative

evidence between mepolizumab and reslizumab; secondly, the inclusion criteria for the mepolizumab and reslizumab trials differed in terms of the eosinophil count and the number of exacerbations per year. This has resulted in different populations being used for these appraisals and thus limits the possibility of consistency in the recommendations of the two appraisals. Further, comparison between technology appraisals is difficult due to the differences in the model structures used in the economic modelling.

5 National Institute for Health and Care Excellence Guidance

NICE published the FAD for this technology appraisal in August 2017 and recommended reslizumab for the treatment of eosinophilic asthma inadequately controlled on ICS [1] in patients whose blood eosinophil count has been recorded as 400 cells per microlitre or more and who have had three or more asthma exacerbations in the past 12 months. The recommendation is conditional on the manufacturer providing reslizumab at the agreed PAS.

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

The committee concluded that, compared with placebo, reslizumab is effective in reducing the rate of clinical asthma exacerbations. It noted that there is limited data on the effectiveness of reslizumab in people who are on maintenance corticosteroids, because only 19 and 12% of people in study 3082 and study 3083, respectively, fulfilled this criterion. However, the committee concluded that treatment with reslizumab may be considered for people who are not taking maintenance oral corticosteroids, but that it would be most beneficial for people who have multiple exacerbations despite maintenance oral corticosteroid use.

The committee concluded that study 3082 and study 3083 are relevant to the UK, but that in clinical practice patients considered for reslizumab may have lower eosinophil counts than in the trials and a higher percentage will be on oral corticosteroids.

At the Appraisal Committee Meeting, clinical experts stated that they would particularly like to have this treatment available for patients taking maintenance oral corticosteroids who have three or more exacerbations per year. However, the committee considered that it was a limitation of the clinical trial that the trial was for 1 year only, which may not necessarily be indicative of future exacerbation rates since event rates vary in patients from year to year.

The committee concluded that the results from the manufacturer's indirect comparison of reslizumab with

omalizumab were highly uncertain and not suitable for decision making. The committee therefore did not consider this comparison further.

The committee concluded the calculation and choice of exacerbation transition probabilities was the key driver of cost effectiveness for reslizumab compared with BSC. It preferred to use results from a model, which used the observed (unadjusted) exacerbation data from the relevant subgroup in the trials to determine the transition probabilities.

In response to the concerns raised in the initial ACD, the manufacturer provided an analysis using the observed (unadjusted) exacerbation rate, adjusting the severe exacerbation utility and health state costs as suggested by the ERG, and proposed a revised PAS, leading to an ICER of £29,870 per QALY gained. The committee noted that the economic model had not included the oral corticosteroid effect of reslizumab and therefore the most plausible ICER could be slightly lower. The committee therefore considered reslizumab a cost-effective use of NHS resources in this patient group.

6 Conclusions

The primary evidence for this STA process came from the 3082 and 3083 randomised, placebo-controlled trials. The evidence suggests that reslizumab is more effective at reducing the rate of clinical asthma exacerbations than BSC for patients with eosinophilic asthma inadequately controlled by ICS. The economic modelling suggests that reslizumab is a cost-effective use of NHS resources provided that reslizumab is offered to the NHS with the agreed confidential PAS.

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Author contributions KC and MR critically appraised the health economic systematic review, critically appraised the economic evaluation and drafted the report. PH and KP critically appraised the clinical effectiveness systematic review and drafted the report. MC critically appraised the economic evaluation and drafted the report. GF critically appraised the clinical effectiveness systematic review, drafted the report, project managed the review and is the project guarantor. This summary has not been externally reviewed by PharmacoEconomics.

Compliance with Ethical Standards

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Conflict of interest All authors (KC, GF, PH, MR, MC and KP) had no conflicts of interest.

References

1. National Institute for Health and Care Excellence. Asthma (eosinophilic)—reslizumab (after inhaled corticosteroids). 2017. <https://www.nice.org.uk/guidance/ta479>. Accessed Oct 2017.
2. National Institute for Health and Care Excellence. 2017. <https://www.nice.org.uk/>. Accessed Oct 2017.
3. Asthma UK. Asthma facts and statistics. 2016. <https://www.asthma.org.uk/about/media/facts-and-statistics/>. Accessed Oct 2017.
4. Asthma UK. 2017. <https://www.asthma.org.uk/about/media/news/asthma-uk-study-1.1bn/>. Accessed Oct 2017.
5. European Respiratory Society (ERS). Assessing asthma quality of life: its role in clinical practice. 2005. <http://breathe.ersjournals.com/content/breathe/1/3/192.full.pdf>. Accessed Oct 2017.
6. British Thoracic Society and Scottish Intercollegiate Guidelines Network. SIGN 141. British Guideline on the Management of Asthma. 2014.
7. Global Initiative for Asthma. Global strategy for asthma management and prevention (2016 update). 2016. http://ginasthma.org/wp-content/uploads/2016/04/GINA-2016-main-report_track-ed.pdf. Accessed Oct 2017.
8. Novelli F, Lenzini G, Latorre M, Seccia V, Bartoli ML, Malagrino L, et al. Influence of obesity and nasal polyps on severe asthma. *Eur Respir J*. 2013;42(Suppl. 57):P4177.
9. Chang PJ, Bhavsar PK, Michaeloudes C, Khorasani N, Chung KF. Corticosteroid insensitivity of chemokine expression in airway smooth muscle of patients with severe asthma. *J Allergy Clin Immunol*. 2012;130(4):877–85.
10. Humbert M, Beasley R, Ayres J, Slavin R, Hebert J, Bousquet J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy*. 2005;60(3):309–16.
11. Castro M, Zangrilli J, Wechsler M, Bateman E, Brusselle G, Bardin P, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multi-centre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med*. 2015;3:355–66.
12. Bjermer L, Lemiere C, Maspero J, Weiss S, Zangrilli J, Germiano M. Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: a randomized phase 3 study. *Chest*. 2016;150(4):789–98.
13. Corren J, Weinstein S, Janka L, Zangrilli J, Garin M. Phase 3 study of reslizumab in patients with poorly controlled asthma: effects across a broad range of eosinophil counts. *Chest*. 2016;150(4):799–810.
14. Castro M, Mathur S, Hargreave F, Boulet L-P, Xie F, Young J, et al. Reslizumab for poorly controlled, eosinophilic asthma. A randomized, placebo-controlled study. *Am J Respir Crit Care Med*. 2011;184:1126–32.
15. Hanania N, Wenzel S, Rosen K, Hsieh H-J, Mosesova S, Choy D, et al. Exploring the effects of omalizumab in allergic asthma. *Am J Respir Crit Care Med*. 2013;187(8):804–11.
16. Willson J, Bateman ED, Pavord I, Lloyd A, Krivasi T, Esser D. Cost effectiveness of tiotropium in patients with asthma poorly controlled on inhaled glucocorticosteroids and long-acting beta-agonists. *Appl Health Econ Health Policy*. 2014;12(4):447–59.
17. Lloyd A, Price D, Brown R. The impact of asthma exacerbations on health-related quality of life in moderate to severe asthma patients in the UK. *Prim Care Respir J*. 2007;16(1):22–7.
18. National Institute for Health and Care Excellence. Single Technology Appraisal. Mepolizumab for treating severe eosinophilic asthma [ID798]. Committee papers 2016. <https://www.nice.org.uk/guidance/ta431>. Accessed Oct 2017.