NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Reslizumab for treating eosinophilic asthma inadequately controlled on inhaled corticosteroids [ID872]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Reslizumab for treating eosinophilic asthma inadequately controlled on inhaled corticosteroids [ID872]

Contents:

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

Contains AIC, CIC

Pre-meeting briefing
Reslizumab for treating asthma with elevated blood eosinophils inadequately controlled by inhaled corticosteroids [ID872]

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal.

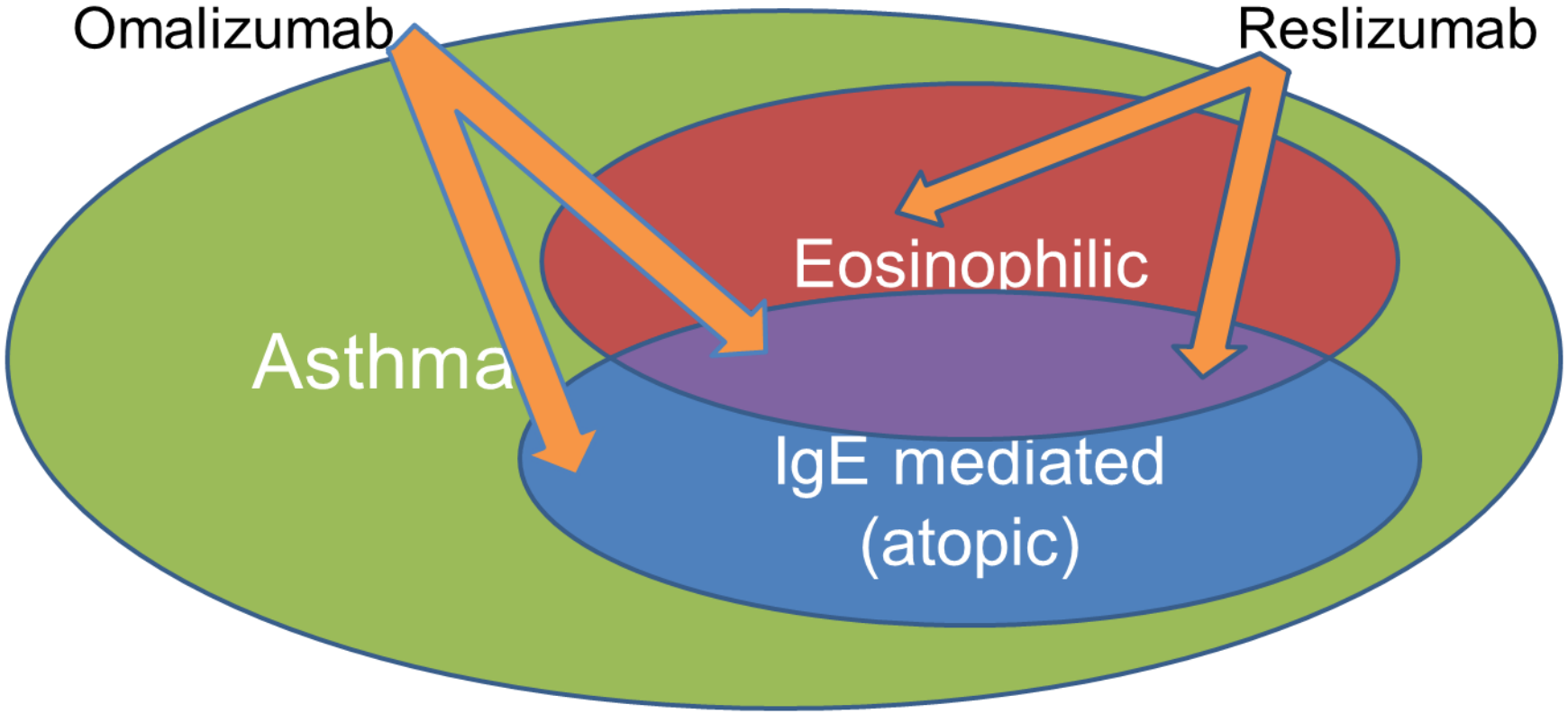
Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting.

Disease Background

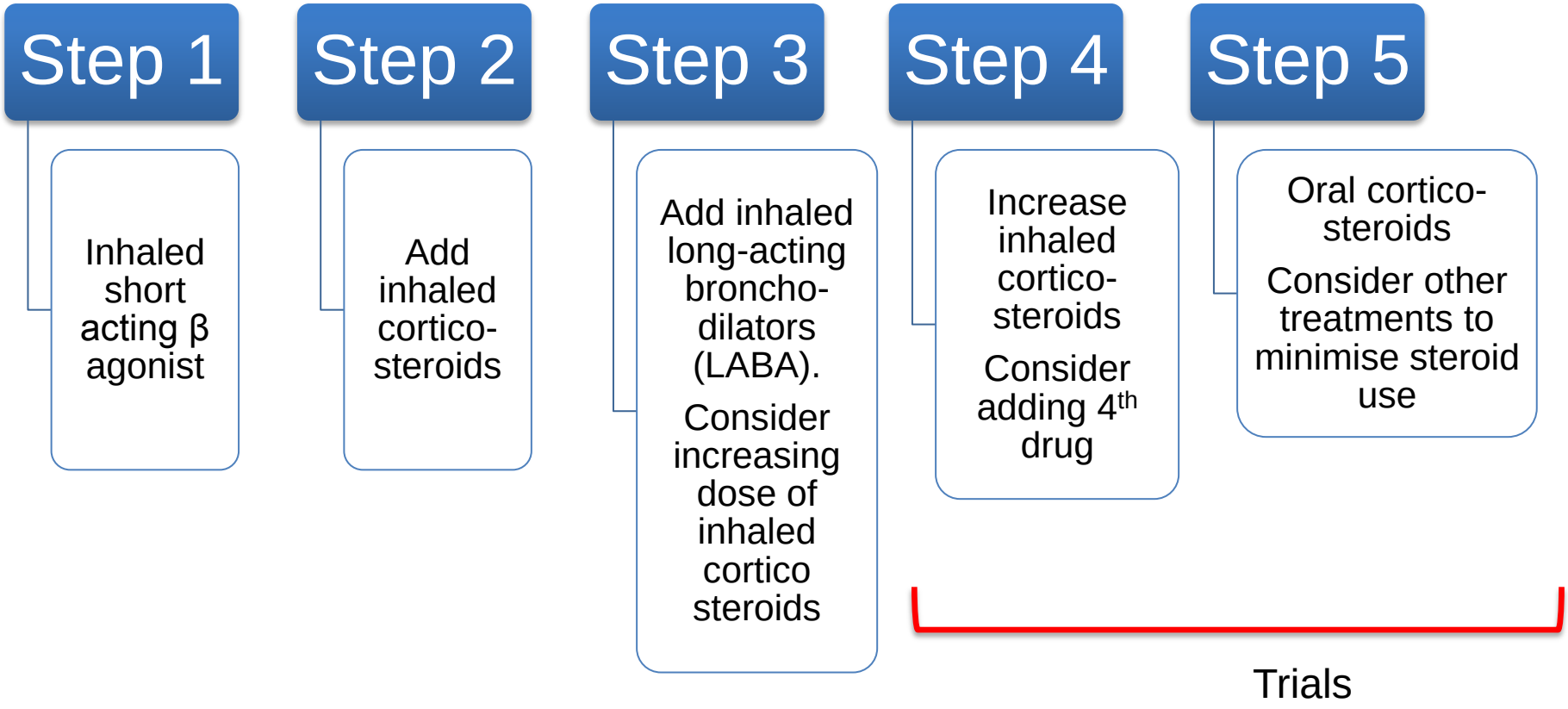
- Asthma is a disease of airway inflammation with associated airflow limitation and hyper responsiveness to intrinsic and extrinsic stimuli
- 5.4 million people in England and Wales receive treatment for asthma
- In 2014, there were 1,133 asthma related deaths in the UK
- 5-10% people have severe asthma
- Severe asthma defined as:
  - ‘asthma that requires treatment with high dose inhaled corticosteroids plus a second controller and/or systemic corticosteroids to prevent it from becoming ‘uncontrolled’ or that remains ‘uncontrolled’ despite this therapy’ (British Thoracic BTS/SIGN Guideline)

Types of severe asthma



- Eosinophilic and IgE-mediated asthma 2 phenotypes of severe asthma
  - Eosinophilic asthma is mediated by IL-5

Global Initiative for Asthma (GINA)
British Guideline Management Asthma
British Thoracic Society Scottish Intercollegiate Guidelines



Technology

Details of the technology	Reslizumab (Cinquaero, Teva)
Marketing authorisation	It is indicated as add-on therapy in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment European marketing authorisation was granted in August 2016
Mechanism of action	Inhibits interleukin-5 which reduces eosinophil numbers and activity
Administration	Intravenous infusion 3mg/kg body weight once every 4 weeks
Acquisition cost	Anticipated list price £499.99 (100 mg vial); £124.99 (25 mg vial). The company has recently submitted a PAS which has not yet been approved by the DH.

Final scope	Company Decision Problem
Adults with asthma with elevated blood eosinophils inadequately controlled by inhaled corticosteroids	Adults with severe refractory eosinophilic asthma + a blood eosinophil count of ≥400 cells/μL; GINA Steps 4 and 5 who had experienced ≥3 asthma exacerbations in the preceding year
Reslizumab + best standard care	
• Best standard care • Omalizumab for severe allergic IgE-mediated eosinophilic asthma subgroup	
• asthma control • clinically significant exacerbations, including unscheduled healthcare • Lung function • Use of oral corticosteroids • Patient and clinician evaluation of Response • Mortality • Time to discontinuation • Adverse effects of treatment • Health-related quality of life.	• Asthma control and symptoms • Clinical asthma exacerbations • Lung function • Short acting beta agonists use (rescue medication) • Blood eosinophil count • Adverse effects of treatment • Health-related quality of life Oral corticosteroid use was not included as patients in trial had to remain on stable dose throughout

• People who require maintenance OCS treatment
• People who require frequent OCS treatment
	• Subgroups - Adults with severe eosinophilic asthma, GINA Steps 4 and 5 who had experienced:
	  • ≥2 exacerbations or
	  • ≥4 exacerbations

Expert Comments

- Corticosteroids very effective for eosinophilic asthma, but have long-term adverse effects; ‘a steroid sparing agent is desperately required’
- Population is ‘BTS stage 4/5 with eosinophilia.’
  - But, need to decide ‘on what eosinophil count is counted as high.’
  - Patients in the trials were highly selected based on an eosinophil count and number of prior exacerbations chosen by company
- Patients likely to be people with uncontrolled eosinophilic asthma which is prone to exacerbation requiring unplanned care
- The length of time needed to establish responsiveness is arbitrary, although experience suggests that it is one year (6 month intervals was also suggested)
- Omalizumab targets atopic (IgE) asthma. Reslizumab targets eosinophilic (IL-5) asthma. These are different populations.
- IL-5 inhibition may lead to rare effects such as parasitic infections and possibly cancer
- If recommended, reslizumab should be limited to specialist centres
- Regarding ‘extra resources’, ongoing surveillance for infection and malignancy should be maintained

British Thoracic Society, British Society for Allergy and Clinical Immunology

Patient/carer perspective 1

- Severe asthma is a cluster of types of asthma that do not respond to standard treatment, rather than simply an extreme form of the condition
- Severe asthma is distressing, socially isolating and potentially life-threatening (Quote 1)
- Patients often cannot breathe well enough to walk or go to work (Quote 2)
- Patients live in fear because ordinary factors like dust, air fresheners, fragrances, pollen, rain, or a common cold can trigger a life threatening attack.
- The result is a substantial psychological and economic burden for patients, family and carers with relationships often suffering..

Patient/carer perspective 2

- Patients want to keep symptoms under control
- They would like to avoid taking very high doses of medicines for a long time
- Patients are also aware of the short term and long term adverse effects of steroids (Quote 3)
- Reducing the use of oral corticosteroid is a key priority for patients
- The impact of caring for someone with severe asthma can be substantial. A major concern is that children can at times be involved as patients or carers

Clinical effectiveness

Reslizumab clinical studies

Phase III studies			
Study 3082	Patients aged 12–75 years with asthma and elevated blood eosinophils (≥400/μL) inadequately controlled with medium to high dose ICS	**Reslizumab 3.0 mg/kg**	Placebo
Study 3083		**Reslizumab 3.0 mg/kg**	
Study 3081		Reslizumab 0.3 mg/kg; reslizumab 3.0 mg/kg	
Study 3084	Adult patients with moderate to severe asthma uncontrolled with medium to high dose ICS	Reslizumab 3.0 mg/kg	Placebo
Phase II studies			
Res-5-0010	Adult patients with asthma and eosinophilic airway inflammation (sputum eosinophils ≥3%)	Reslizumab 3.0 mg/kg	Placebo

Pivotal reslizumab studies

- Studies 3082 and 3083 provide the core efficacy evidence.
- 3082 and 3083 were identical in design
  - evaluated reslizumab 3.0 mg/kg administered every 4 weeks over 52 weeks in people with eosinophil levels ≥400 cells/µL.
- 3081 evaluated reslizumab 0.3 mg/kg and 3.0 mg/kg administered every 4 weeks over 16 weeks

Supporting evidence

- 3084 evaluated reslizumab 3.0 mg/kg administered every 4 weeks for 16 weeks in patients with moderate to severe asthma with eosinophil levels ≥400 cells/µL
- 3085 was an open-label, long-term safety extension of studies 3081, 3082 and 3083
- 3082, 3083, 3081 and 3085 included patients aged 12-75 years (although mean age from main trials was 44-47 years)
- 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

Outcomes and direct meta-analysis of reslizumab vs placebo trials

- Asthma control questionnaire (ACQ) score
- Exacerbations
- Lung Function (Change in FEV_1)
- Health-related quality of life - Asthma Quality of Life Questionnaire (AQLQ)

- Company used a frequentist model (using both random and fixed effect) for all outcomes except exacerbations for which the company used a Bayesian approach
- inverse variance-weighted method was used to analyse binary and continuous outcomes
- least squares method was used to estimate the between study variance for random effects model

Results from direct comparison meta-analysis Changes in lung function (FEV1)

FEV_1: 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	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.
FEV_1: mean change from baseline (L) at 52 week				
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

Direct comparison meta-analysis: FEV1 change over 16 and 52 weeks			
Meta-analysis	Difference between means, reslizumab vs placebo (95% CI)		Source
	16±1 weeks	52 weeks	CS Tables 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%	

Results from direct comparison meta-analysis ACQ score (reslizumab vs placebo)

ACQ score: mean change from baseline at 16±1 weeks				
Trial	**Reslizumab**	**Placebo**	**Mean difference (95% CI)**	**Source**
3082	-0.94 (n=242)	-0.68 (n=241)	-0.27 (-0.40, -0.13); p=0.0001	CS Table 25
3083	-0.86 (n=230)	-0.66 (n=228)	-0.20 (-0.33, -0.07); p=0.0032	CS Table 35
3081	-0.94 (n=91)	-0.58 (n=84)	-0.35 (-0.63, 0.08); p=0.0129	CS Table 47
3084	-0.91 (n=343)	-0.70 (n=83)	-0.20 (-0.39, -0.004); p=0.0457	CS Table 55
Res-5-0010	-0.7 (n=53)	-0.3 (n=53)	-0.38 (-0.76, 0.01); p=0.054	Castro et al.

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%	

Results for exacerbations (reslizumab versus placebo)

Trial	Adjusted mean frequency		Rate ratio (95% CI)	Source
	Reslizumab	Placebo		
Rate of clinical asthma exacerbations over 52 weeks				
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
Exacerbations requiring oral corticosteroids for ≥3 days over 52 weeks				
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
Exacerbations requiring hospitalisation and/or emergency visit over 52 weeks				
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

Clinically significant exacerbations (reslizumab versus placebo)

Study, Follow up	Reslizumab versus placebo				
	Treatment arm	N	Exacerbation rate	Number of exacerbations	Person-years
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
Res-05-0010, over 15 weeks	Reslizumab	53	NR	4	15.29
	Placebo	53	NR	10	15.29

See CS table 67

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	

See CS table 68

Health-related quality of life (AQLQ score)

(reslizumab versus placebo)

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 (n=99)	0.78 (n=101)	0.36 (0.05, 0.67); p=0.0241	CS Table 48
AQLQ score: mean change from baseline at 52 weeks				
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

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%	

Adverse events

	3082		3083	
AEs, n (%)	**Reslizumab 3.0 mg/kg N=245**	**Placebo N=243**	**Reslizumab 3.0 mg/kg N=232**	**Placebo N=232**
Any AEs	197 (80)	206 (85)	177 (76)	201 (87)
Mild	68 (28)	41 (17)	67 (29)	36 (16)
Moderate	107 (44)	133 (55)	98 (42)	140 (60)
Severe	22 (9)	32 (13)	12 (5)	25 (11)
Treatment-related AEs‡	36 (15)	36 (15)	34 (15)	27 (12)
Mild	24 (10)	23 (9)	22 (9)	14 (6)
Moderate	9 (4)	13 (5)	11 (5)	13 (6)
Severe	3 (1)	0	1 (<1)	0
SAEs	24 (10)	34 (14)	18 (8)	23 (10)
Deaths	0	1 (<1)	0	0
AE leading to discontinuation	4 (2)	8 (3)	8 (3)	9 (4)

Most common AEs (>20%) included: asthma, upper respiratory tract infection, nasopharyngitis, sinusitis, headache, influenza and bronchitis

Indirect treatment comparison

For comparison of reslizumab with omalizumab only (allergic asthma with elevated eosinophils)

- 16 omalizumab studies identified for indirect comparison (a maximum of 4 studies were used per outcome)
- The results of the ITC suggest that most outcomes did not differ between reslizumab and omalizumab with the exception of:
  - Clinical significant exacerbations (favoured reslizumab)
  - AQLQ (favoured omalizumab at 16 weeks, but no difference at 52 weeks)
- 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
- The results of the ITC do not directly inform the company's health economic analysis

ERG comments

- Included trials are of generally high quality
- Trials had relatively short duration (52 weeks max – some were 15-16 weeks) considering the chronic nature of severe asthma
- Not all available lung function and health-related quality of life 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
- For most outcomes the sample sizes are smaller than the number of patients randomised
- The indirect treatment comparison assumes the effectiveness of omalizumab in patients with elevated blood eosinophils is the same as that in patients with IgE-mediated asthma; and that placebo in trial is the same as BSC, and that BSC is the same as conventional or optimised asthma therapy or a control group.

Key issues: clinical effectiveness (1)

- Is the clinical effectiveness data from the trials against placebo generalisable to the population being considered?
- Definition based on blood eosinophil count of 400 or more
- Moderate to high dose inhaled corticosteroids
- Low rates of oral corticosteroids
- Two or more exacerbations in the previous year
- Data is only available for 52 weeks from the trials: would the benefit continue longer term?

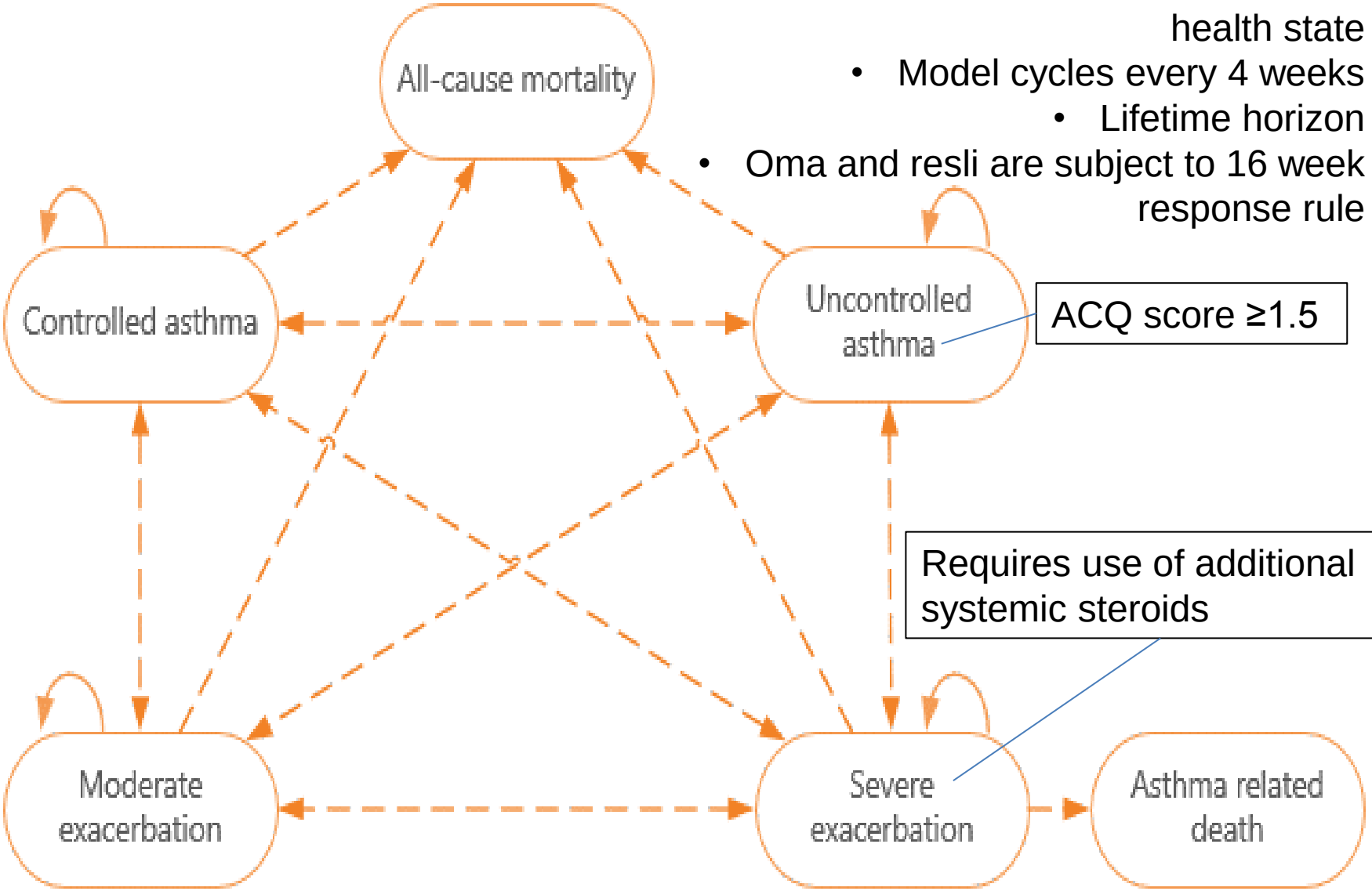
Key issues: clinical effectiveness (2)

- Placebo was the comparator in the trials. What would be the alternative treatments for these patients in clinical practice?
  - Might they include oral corticosteroids, mepolizumab or omalizumab?
- In patients with both eosinophilia and IgE mediated asthma, where omalizumab might be used, how reliable is the ITC comparing reslizumab with omalizumab?
- Improvement in the placebo arm was seen in the trial – what is the significance of this?

Cost effectiveness evidence

Model structure

- Patients enter in uncontrolled asthma health state
- Model cycles every 4 weeks
- Lifetime horizon
- Oma and resli are subject to 16 week response rule



Model details

- Company selected a subgroup for their base case for reslizumab vs BSC:
  - Adults with purely eosinophilic asthma
  - At GINA 4/5 with 3 or more exacerbations in the last year.
- Other groups considered as part of scenario analyses were:
  - Adults GINA 4/5 with 2 or more exacerbations
  - Adults GINA 4/5 with 4 or more exacerbations
- Company also compared reslizumab vs omalizumab in people with eosinophilia linked to allergic asthma

Model details continued

- 60 year time horizon
- Model contains stopping rules for reslizumab and omalizumab
  - [redacted]
  - patients assessed every year (as per reslizumab SmPC)
- The model does not include stopping of oral corticosteroids, as the pivotal trials did not allow it.
- The company had utility data from trials, but did not use them instead chose values from the literature

Clinical data used in model

Variable	Value	Reference
Time horizon	60 years	NICE reference
Discount rates (costs and outcomes)	Costs: 3.5% Outcomes: 3.5%	
Age	46.8 years	Pooled analysis of reslizumab studies 3082 and 3083, adult patients at GINA Step 4/5
% male	37%	
Average weight	75.2 kg	
% of severe exacerbations - reslizumab	76.3%	
% of severe exacerbations – BSC	81.8%	
% patients on reslizumab identified as non-responders at 16 weeks	13.2%	Analysis of reslizumab studies 3082 and 3083, patients with ≥2 prior exacerbations
% of severe exacerbations leading to hospitalisation across arms	24.8%	Data on file provided by clinical expert, UK cohort of severe asthma patients
% of non-responders to omalizumab at 16 weeks	43.5%	Omalizumab HTA
Relative rate of exacerbations in responders to omalizumab vs BSC	0.373	Omalizumab HTA
Relative treatment effect of reslizumab vs BSC		Taken directly from 3082 and 3083

Transition probabilities

- Computed using patient level data from the 2 pivotal reslizumab clinical trials (studies 3082 and 3083)
- In the company's base case analyses, the transition probabilities used were for patients having experienced ≥2 exacerbations (in the preceding year) (CS p186).
  - the baseline risk of exacerbation was then multiplied by 2.15 and then referred to as 'patients having experienced ≥ 3 exacerbations in the preceding year'
- The transition probabilities for the patients having experienced ≥3 exacerbations were not used because the company felt they were 'not considered robust'
- A scenario analysis was run based on the transition probabilities estimated on all adult patients GINA 4/5 which corresponds to the trial population.

Placebo response

- ACQ responder analysis results were 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.
- the analysis is limited as it was not controlled for multiple testing and ERG is unclear whether it was planned or post-hoc
- 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

Multiplier used to adjust exacerbation probabilities

- The company used a multiplier
  - 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) and
  - 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 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.
  - The ERG states that it is 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 a more meaningful reflection of uncertainties over the absolute and relative risks in the probabilistic sensitivity analysis (company did this for omalizumab arm of model).

Exacerbation multiplier

- Pivotal trials ran for 1 year each; no asthma-related deaths were reported.
- Company used 0.42 as relative rate of exacerbation of reslizumab (for patients still on treatment) versus BSC
  - Similar to meta-analysis results 0.44 [0.35;0.56] from fixed effects model
- ERG concerned that base case analysis overestimates the BSC exacerbation rate due to the use of a multiplier for the exacerbation probability

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	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

ERG table 68, pg. 127

Health-related quality of life

- For the base case, published estimates based on EQ-5D data were selected.
- AQLQ mapped to EQ-5D was used as part of a scenario analysis.

Health state	Utility value	95% CI	Reference in submission	Justification
Uncontrolled asthma	0.728	0.707; 0.749	Willson et al, 2014	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	
Severe exacerbation	0.33	0.309; 0.351	Willson et al, 2014	

See table 115, CS page 201.

Costs

Reslizumab	£499.99 per 100 mg vial	Teva UK Limited, list price
Reslizumab	£124.99 per 25 mg vial	Teva UK Limited, list price
Omalizumab	£128.07 per 75 mg pre-filled syringe	BNF listed price
Fluticasone propionate + Salmeterol	£40.92	
Salbutamol	£1.50	
Specialist nurse	£59 per hour	NHS reference costs 2014/2015
Specialist visit	£146.53	
Administrations of omalizumab per cycle	1.31	Omalizumab HTA
Time for administration and monitoring	Omalizumab: 40 mins Reslizumab: 55 mins	Clinical experts
Cost per health state (excluding drug costs)		
Controlled asthma	£11.86	Willson et al, 2014 and unit costs taken from NHS reference costs, PSSRU and BNF – see CS Table 118 and Table 121
Uncontrolled asthma	£45.19	
Moderate exacerbation	£70.36	
Severe exacerbation	£649.56 Severe exacerbation not leading to hospitalisation: £234.21 Severe exacerbation not leading to hospitalisation: £1,906.54	

Company's base case deterministic results, using list prices for reslizumab and omalizumab

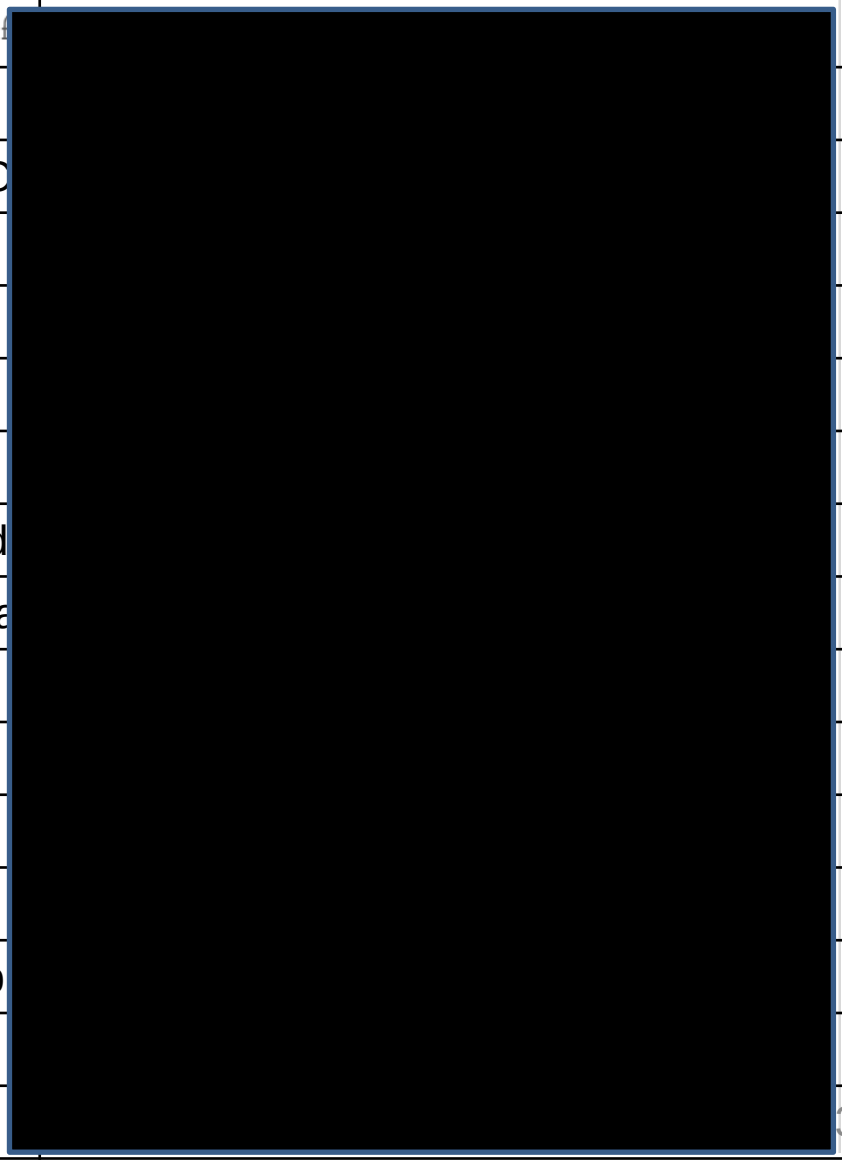
:

Treatment arm	Total			Incremental			ICER/ QALYs, £
	Costs, £	LY	QALYs	Costs, £	LYG	QALYs	
Company's base case: Patients with a history of ≥3 exacerbations							
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Reslizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with severe persistent allergic IgE-mediated eosinophilic asthma and a history of ≥3 exacerbations							
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Omalizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reslizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Contains CIC

Tornado diagram (reslizumab vs BSC)

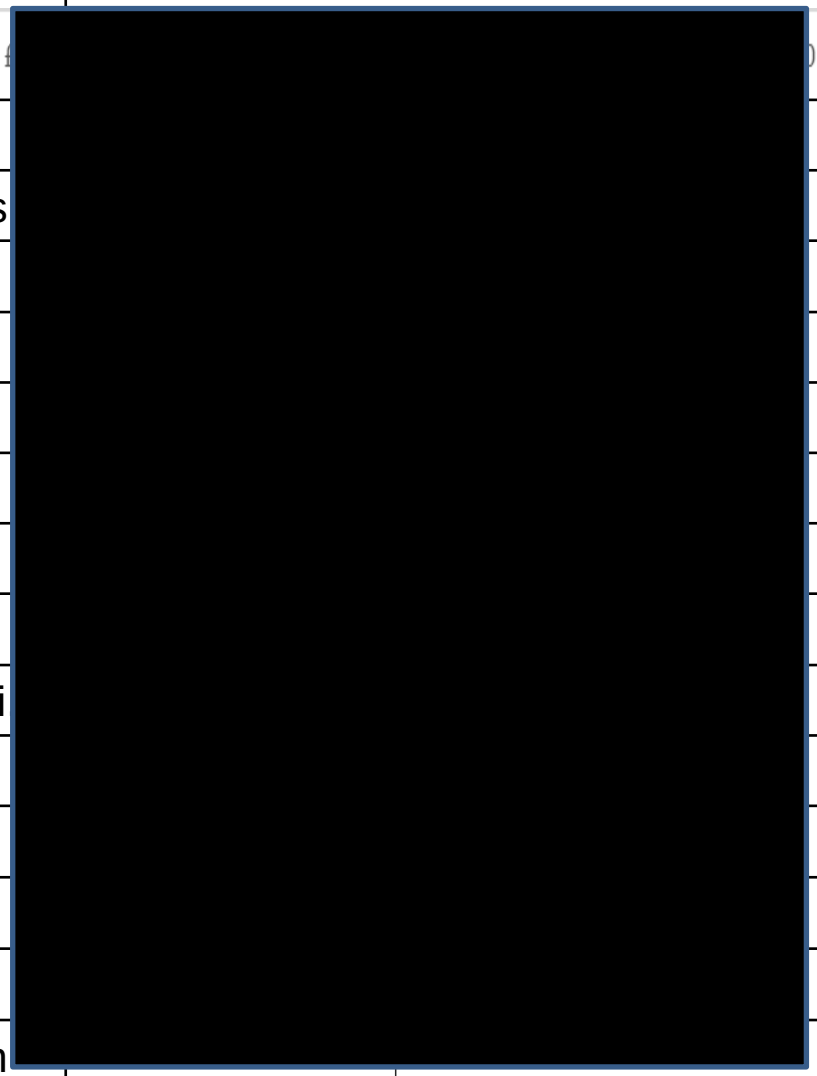
Base Case	Min - Max	Contains CIC
60 yrs	5 - 60	Time horizon
4.67	4.29 – 5.05	Ann. rate of exacer. BSC
Varied by age		OR asthma death
3.5	0 – 5%	Discount rate
46.8	37.4 -56.2	Patient age
9.58	9.08 -10.08	Weight (number of vials)
24.8%	19.9 - 29.8	% severe - > hospitalised
0.92	0.90 - 0.94	Utility – controlled asthma
£649	£520 - 779	Cost – severe exacer.
18.2%	14.6 - 21.6	% moderate - BSC
£649	£520 - 779	Cost – severe exacer.
0.33	0.31 - 0.35	Utility – severe exacer.
23.7%	19 - 28.4	% moderate - reslizumab
0.57	0.55 -0.59	Utility – mod. exacer.
63%	50.5 -75.6	% female



Tornado diagram (reslizumab vs omalizumab)

Contains CIC

Base Case	Min - Max	
60 yrs	5 - 60	Time horizon
0.82	0.41 - 1.61	RR oma vs BSC post weeks
4.67	4.29 - 5.05	Ann. rate of exacer. BSC
Varied by age		OR asthma death
46.8	37.4 -56.2	Patient age
3.5	0 – 5%	Discount rate
9.58	9.08 - 10.08	Weight (number of vials)
24.84%	19.9 - 29.8	% severe - hospitalisation
13.2%	8.2 - 18.2	Early non-responders – resli
0.92	0.90 - 0.94	Utility – controlled asthma
£649	£520 - 779	Cost – severe exacerbation
£649	£520 - 779	Cost – severe exacerbation
0.37	0.27 - 0.52	RR oma vs BSC pre 16 wks
0.33	0.31 - 0.35	Utility – severe exacerbation



Company's probabilistic base case, using list prices

Reslizumab vs. BSC		Reslizumab vs. omalizumab	
Deterministic Base case ICER	PSA ICER	Deterministic Base case ICER	PSA ICER
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

Contains CIC

Company's subgroup analyses, using list prices

Treatment arm	Total			Incremental			ICER/ QALY, £
	Costs, £	LYG	QALYs	Costs, £	LYG	QALYs	
Company's base case: Patients with a history of ≥3 exacerbations							
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reslizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients having experienced ≥2 exacerbations							
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reslizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients having experienced ≥4 exacerbations							
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reslizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Contains CIC

ERG comments

- Model structure adopted for the economic evaluation is generally appropriate and consistent with the clinical disease pathway, although different from model used in omalizumab and mepolizumab – which made comparison difficult
- BSC was not well defined in model
- Model uses transition probabilities derived from large, good quality trials for reslizumab vs BSC
  - 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
- Is it appropriate to calibrate the model to increase the number of exacerbations to a similar level as seen in the year preceding the trial?
- ERG had concerns about the company's 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

ERG's exploratory analyses - changes to exacerbation multiplier using list prices for treatments

Scenario	Treatment	Total costs	Total QALYs	ICER (£/QALY)
Company's base case, Patients with history ≥2 exacerbations of multiplier = 2.15	BSC	[redacted]	[redacted]	[redacted]
	Omalizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]
ERG's analysis, Patients with history of ≥2 exacerbations, multiplier = 1)	BSC	[redacted]	[redacted]	[redacted]
	Omalizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]

Contains CIC

Contains CIC

ERG's exploratory analyses – utility values, using list prices

Health State	Ratio to baseline	Base case	Utility Scenario 1	Utility Scenario 2	Utility scenario 3
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

Scenario	Treatment	Total costs	Total QALYs	ICER (£/QALY)
Company base case	BSC	[redacted]	[redacted]	[redacted]
	Omalizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]
Utility scenario 1;	BSC	[redacted]	[redacted]	[redacted]
	Omalizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]
Utility scenario 2;	BSC	[redacted]	[redacted]	[redacted]
	Omalizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]
Utility scenario 3;	BSC	[redacted]	[redacted]	[redacted]
	Omalizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]

ERG's additional exploratory analyses

- The ERG conducted further analyses
  - scenario analysis was undertaken with the alternative health state costs
  - using the monitoring time used in the NICE MTA appraisal for omalizumab

- Neither of these resulted in major changes to the company's base case ICER

ERG's revised base case analyses, using list prices

Contains CIC

Scenario	Treatment	Total costs	Total QALYs	ICER (£/QALY) vs BSC
Company's base case	BSC	[redacted]	[redacted]	[redacted]
	Omalizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]
ERG's preferred base case	BSC	[redacted]	[redacted]	[redacted]
	Omalizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]

The ERG preferred base case includes:

- Patients ≥ 2 exacerbations; multiplier = 1;
- change in exacerbation rate for BSC (exacerbation multiplier =1)
- applying the disutilitiies from Lloyd et alto the uncontrolled health state to derive the exacerbation utility values
- change in health state costs and change in monitoring duration for omalizumab.

Innovation

- Currently very few treatments for severe refractory eosinophilic (IL-5 mediated) asthma who are not eligible for omalizumab
- Long term use of corticosteroid has severe adverse effects

Potential equality issues

- None identified at scoping stage or in submissions.

Key issues: cost effectiveness (1)

- The company chose to use a subgroup of patients with 3 or more exacerbations in the previous year as the base-case, what is the committee's view of the appropriateness of this?
- The company model includes two stopping rules, one at 16 weeks and one at 52 weeks, are these appropriate?
- The company noted the placebo effect and adjusted for this in both arms of the trial rather than using direct trial data. This was done by adjusting the observed rate of exacerbations in the trials by a factor derived from the pre-trial BSC exacerbation rate, further adjusted for the 3 or more exacerbation subgroup. This adjustment was applied to both arms

Key issues: cost effectiveness (2)

- The ERG had concerns over the rationale for this adjustment, and also the explanation given as to how it was derived, what is the committee's view on this?
- The company did not use utility data from the trials, but used mixed literature sources for health-related quality of life. Are these applicable and appropriate?
- What is the committee's view of the cost effectiveness of reslizumab compared with omalizumab in the 'overlap' population?

Authors

- **Richard Diaz**
  Technical Lead
- **Joanna Richardson**
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- with input from the Lead Team (Jeremy Braybrooke, David Thomson and Stephen Sharp)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Reslizumab for treating asthma with elevated blood eosinophils inadequately controlled by inhaled corticosteroids [ID872]

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of reslizumab within its marketing authorisation for treating asthma with elevated blood eosinophils inadequately controlled by inhaled corticosteroids.

Background

Asthma is a chronic inflammatory disease associated with variable airflow obstruction and airway hyperresponsiveness. It is characterised by exacerbations associated with symptoms such as breathlessness, chest tightness, wheezing, sputum production and cough. Severe eosinophilic asthma is a subset of the condition that is associated with blood and sputum elevated eosinophils and recurrent exacerbations. Eosinophilic nasal polyps may also be present. Eosinophils are thought to play a major role in airway inflammation in asthma.

People with severe asthma often have a severely impaired quality of life which can lead to fatigue, absence from school or work and psychological problems including stress, anxiety and depression. There were 1242 deaths from asthma in the UK in 2012.[1] Estimates suggest that around 5.4 million people in England and Wales currently receive treatment for asthma.

Current British guidelines from the British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) recommend a stepwise approach to treatment in adults. Control is maintained by stepping up treatment as necessary and stepping down when control is good. The guideline steps are summarised as follows:

- Step 1. Inhaled short-acting beta-2 agonist as required.
- Step 2. Add inhaled corticosteroid (200–800 micrograms per day).
- Step 3. Add an inhaled long-acting beta-2 agonist. If control remains inadequate, increase the dose of the inhaled corticosteroid to 800 micrograms per day. If there is no response to the inhaled long-acting beta-2 agonist, stop this drug and increasing the inhaled corticosteroid dose 800 micrograms per day. If control is still inadequate, try a leukotriene receptor antagonist or slow-release theophylline.

- Step 4: Consider increasing the dose of inhaled corticosteroid up to 2000 micrograms per day. Consider adding a fourth drug (for example, a leukotriene receptor antagonist, slow-release theophylline or a beta-2 agonist tablet).

- Step 5: Use daily steroid tablets at the lowest dose providing adequate control. Maintain high-dose inhaled corticosteroid at 2000 micrograms per day. Consider other treatments to minimise the use of steroid tablets. Refer patients to specialist care.

NICE technology appraisal guidance 278 recommends omalizumab as an option for treating severe persistent allergic IgE-mediated asthma as add-on therapy to optimised standard therapy in people aged 6 years and older who need continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year), and only if the manufacturer makes omalizumab available with the discount agreed in the patient access scheme. Optimised standard therapy is defined in the recommendations as a full trial of and, if tolerated, documented compliance with inhaled high-dose corticosteroids, long-acting beta2 agonists, leukotriene receptor antagonists, theophyllines, oral corticosteroids, and smoking cessation if clinically appropriate.

The technology

Reslizumab (Cinquil, Teva Pharmaceuticals) is an anti-interleukin-5 monoclonal antibody. By reducing the effects of interleukin-5, reslizumab causes a reduction in circulating eosinophils, a type of white blood cell involved in allergic response and tissue inflammation. Reslizumab is administered intravenously in addition to best standard asthma care.

Reslizumab does not currently have a marketing authorisation in the UK for treating asthma with elevated blood eosinophils inadequately controlled by inhaled corticosteroids. Reslizumab has been studied in clinical trials in comparison with placebo in people aged 12–75 years with asthma with elevated blood eosinophils inadequately controlled by inhaled corticosteroids.

Intervention(s)	Reslizumab (in addition to best standard care)
Population(s)	Adults with asthma with elevated blood eosinophils inadequately controlled by inhaled corticosteroids
Comparators	• Best standard care without reslizumab For people with severe persistent allergic IgE-mediated asthma with elevated blood eosinophils: • Omalizumab

Outcomes	The outcome measures to be considered include: • asthma control • incidence of clinically significant exacerbations, including those which require unscheduled contact with healthcare professionals or hospitalisation • use of oral corticosteroids • patient and clinician evaluation of response • lung function • mortality • time to discontinuation • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.

Other considerations	Best standard care for this population is considered to be step 4 and/or step 5 in the stepwise approach to treatment from the SIGN/BTS guideline (for example, high-dose inhaled corticosteroids and oral corticosteroids). If the evidence allows, the following subgroups will be considered: • People who require maintenance oral corticosteroid treatment • People who require frequent oral corticosteroid treatment. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals:** 'Omalizumab for treating severe persistent allergic asthma (review of technology appraisal guidance 133 and 201)' (2013) NICE technology appraisal 278. Review proposal date currently being reviewed. 'Inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over' (2008) NICE technology appraisal 138. Guidance on static list. **Appraisals in development:** 'Mepolizumab for treating severe eosinophilic asthma' NICE technology appraisal guidance [ID798]. Publication expected July 2016. **Guidelines in development:** 'Asthma – diagnosis and monitoring'. Publication date to be confirmed. 'Asthma management'. Publication expected June 2017. **Related Interventional Procedures:** 'Bronchial thermoplasty for severe asthma' (2012). NICE interventional procedures guidance 419, **Related Quality Standards:** 'Asthma' (2013) NICE quality standard 25.

	Related NICE Pathways: Asthma (2014). http://pathways.nice.org.uk/pathways/asthma
Related National Policy	NHS England (January 2014) Adult Highly specialised respiratory services. Manual for prescribed specialised services 2013/14. NHS England (2014) Internal Medicine's Group: A14. Specialised Respiratory. Department of Health (2014) The NHS Outcomes Framework 2015/16 Domains 1, 2, 3 and 4

References

1. Royal College of Physicians (2014) National review of asthma deaths. Accessed April 2015

Appendix C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Single Technology Appraisal (STA)

Reslizumab for treating eosinophilic asthma inadequately controlled on inhaled corticosteroids [ID872]

Provisional matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Company(ies) • Teva Pharmaceuticals (reslizumab) Patient/carer groups • Action Against Allergy • Action for sick children • Allergy UK • Asthma UK • Black Health Agency • British Lung Foundation • Muslim Council of Britain • National Children's Bureau • South Asian Health Foundation • Specialised Healthcare Alliance • The Anaphylaxis Campaign Professional groups • Association of Respiratory Nurse Specialists • British Geriatrics Society • British Paediatric Respiratory Society • British Society for Allergy & Clinical Immunology • British Thoracic Society • Primary Care Respiratory Society UK • Royal College of General Practitioners • Royal College of Nursing • Royal College of Paediatrics & Child Health • Royal College of Pathologists • Royal College of Physicians • Royal Pharmaceutical Society • Royal Society of Medicine	General • Allied Health Professionals Federation • Asthma Relief Charity • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare Products Regulatory Agency • NARA – The Breathing Charity • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Possible comparator companies • Novartis (omalizumab) Relevant research groups • Asthma, Allergy and Inflammation Research Trust • British Association for Lung Research • Cochrane Airways Group • MRC Clinical Trials Unit • National Institute for Health Research • National Society for Research into Allergy Evidence Review Group

Appendix C

Consultees	**Commentators (no right to submit or appeal)**
• UK Clinical Pharmacy Association <u>Others</u> • Department of Health • NHS England • NHS Knowsley CCG • NHS St Helens CCG • Welsh Government	• National Institute for Health Research Health Technology Assessment Programme <u>Associated Guideline groups</u> • National Clinical Guideline Centre <u>Associated Public Health groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: manufacturers of comparator technologies; Healthcare Improvement Scotland; the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines); other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the *British National Formulary*.

All non-company commentators are invited to nominate clinical specialists or patient experts.

Evidence Review Group (ERG)

An independent academic group commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA Programme) to assist the Appraisal Committee in reviewing the company evidence submission to the Institute.

[1]Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Asthma (eosinophilic) - reslizumab (after inhaled corticosteroids) [ID872]

Company evidence submission

[July 2016]

File name	Version	Contains confidential information	Date
	1.0	Yes	14 July 16

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 250 pages, excluding appendices and the pages covered by this template.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

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Abbreviations

AAAAI	The American Academy of Allergy, Asthma and Immunology
ACQ	Asthma Control Questionnaire
AE	Adverse event
AIDS	Acquired immune deficiency syndrome
ANCOVA	Analysis of covariance
ASUI	Asthma Symptom Utility Index
AQLQ	Asthma Quality of Life Questionnaire
ATS	American Thoracic Society
AWMSG	All Wales Medicines Strategy Group
BMI	Body mass index
BSC	Best standard of care
BTS	British Thoracic Society
CADTH	Canadian Agency for Drugs and Technologies in Health
CAE	Clinical asthma exacerbation
CBC	Complete blood count
CHEST	American College of Chest Physicians
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CPK	Creatine phosphokinase
CT	Computerised tomography
DDI	Drug-drug interaction
DIC	Deviance information criterion
ECG	Electrocardiography
ECP	Eosinophil cationic protein
eCRF	Electronic case report form
EDN	Eosinophil-derived neurotoxin
EEA	European Economic Area
EMA	European Medicines Agency
EP	Eosinophilic peroxidase
EPAR	European public assessment report
EQ-5D	EuroQol 5-dimensions questionnaire
ERS	European Respiratory Society
EU	European Union

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
HAS	Haute Autorité de Santé
HCP	Healthcare professional
HEENT	Head, eyes, ears, nose and throat
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ICS	Inhaled corticosteroid
IgE	Immunoglobulin E
IL-5	Interleukin-5
IRT	Interactive Response Technology
ITT	Intent-to-treat
LABA	Long-acting beta-agonist
LAMA	Long-acting muscarinic-antagonist
LS	Least squares
LTRA	Leukotriene receptor antagonist
MID	Minimally important difference
MMRM	Mixed-effect model for repeated measures
NA	Not applicable
NHWS	National Health and Wellness Survey
NSAID	Non-steroidal anti-inflammatory drug
OCS	Oral corticosteroid
OR	Odds ratio
PEFR	Peak expiratory flow rate
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial

RS	Randomised set
SABA	Short-acting beta-agonist
SAE	Serious adverse event
SAS	Safety analysis set
SD	Standard deviation
SE	Standard error
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SOC	System organ class
TEAE	Treatment-emergent adverse event
WBC	White blood cell

1 Executive summary

1.1 *Statement of the decision problem*

Background and context

Asthma is a common, chronic respiratory disease characterised by reversible airflow obstruction, bronchial hyperresponsiveness and airway inflammation (1). It is one of the most common chronic conditions worldwide, affecting approximately 30 million children and adults in Europe under the age of 45 (2). The number of people affected by asthma in the UK is among the highest in the world; according to the British Lung Foundation and Asthma UK, 8 million people (over 12% of the UK population) have been diagnosed with asthma and around 5.4 million people are currently receiving treatment for the disease: 4.3 million (1 in 12) adults and 1.1 million (1 in 11) children (3, 4). Management of asthma imposes a substantial burden on national healthcare systems; the total cost of asthma in Europe is estimated at €33.9 billion (based on 2011 values for EU countries), with €19.5 billion and €14.4 billion attributable to direct and indirect costs, respectively (5). UK allergy studies have reported direct healthcare expenditure, driven mainly by asthma, of over £1 billion in England and Wales, and in excess of £130 million in Scotland (6, 7).

The prevalence of severe asthma is not well understood, likely due to difficulty in estimating these figures due to disease heterogeneity. However, the proportion is often estimated to be 5–10% of the total asthma population (8). It is increasingly evident that severe asthma is not a single disease, and rather consists of recognisable 'phenotypes' that result from complex interactions between genetic and environmental factors (8, 9). Eosinophilic asthma is a well-recognised phenotype of severe asthma that is associated with elevated levels of eosinophils in the tissue and sputum, and a thickening of the basement membrane (1). Eosinophils have long been recognised to play a major role in airway inflammation in asthma (10); elevated levels are associated with an increased frequency of asthma exacerbations and poor disease control (see Section 3.2.1) and hence there is a need for accurate phenotype identification and targeted treatments in patients with severe eosinophilic asthma.

Asthma exacerbations, which are a prominent feature of poorly-controlled, severe asthma, lead to morbidity and can be fatal (11, 12). The association of elevated eosinophil levels with both exacerbations and more broadly with acute respiratory events is supported by several studies (13-15), and eosinophils have been found to be a major risk factor for frequent exacerbations (12, 16, 17). Patients with severe asthma experience on average 1.99 exacerbations per year; based on the reslizumab trial data, 41.5%, 21.4% and 12.7% of patients with severe asthma experience at least 2, at least 3 and at least 4 exacerbations per year, respectively (18). Asthma accounts for high numbers of consultations in primary care, out-of-hours services and hospital emergency departments; during 2011–2, there were over 65,000 hospital admissions for asthma in the UK (19). In an analysis of asthma mortality rates in UK patients hospitalised for asthma from 2000–2005, the total number of deaths during the 5-year period was 1063 patients from 250,043 hospital admissions (0.43%) (20). A more recent study of mortality rates for adults in Scotland following hospitalisation for asthma from 1981–2009

identified 1000 case fatalities within 30 days of admission from 116,457 asthma admissions during the study period (0.86%) (21).

The overall aim of asthma management is to achieve good disease control with minimal future risk of symptoms and side effects of treatment, and with patients able to lead a normal, active life (9, 22). The British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) British guideline for the management of asthma recommends a stepwise approach to treatment in adults, whereby 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 necessary and stepping down when control is good (see Section 3.3.1) (22). The Global Initiative for Asthma (GINA) recommends a similar stepwise treatment approach to control asthma symptoms and minimise future risk (9). Specific recommendations for the management of the population relevant to the current submission – defined in the NICE scope as adults with asthma and elevated blood eosinophils inadequately controlled by inhaled corticosteroids (ICS) – are currently limited. However, this population is equivalent to patients at Step 4 and/or Step 5 of the BTS/SIGN and GINA treatment pathways, for whom best standard of care (BSC) is high-dose ICS in combination with other controller medications, with or without OCS. This population comes under both the European Respiratory Society/American Thoracic Society (ERS/ATS) Task Force (8) and GINA (9) definitions of severe asthma (see Section 3.1.1 and 3.3).

For patients with severe asthma who remain inadequately controlled with medium to high dose ICS in combination with other controller medications, there are very few treatment options other than continuing to increase the ICS dose or adding OCS (9, 22). Furthermore, prolonged use of high-dose inhaled or systemic corticosteroids is associated with several well-known adverse effects (23-27).In recent years the focus of severe asthma management has shifted towards individualised care and phenotype-targeted biological therapies (8). The anti-IgE monoclonal antibody omalizumab (Xolair) is recommended as an add-on therapy for patients with severe persistent allergic asthma aged six years and older who need continuous or frequent treatment with OCS (24, 28). However, omalizumab does not target the eosinophilic (interleukin-5 [IL-5]-mediated) phenotype and so is unsuitable for patients with severe eosinophilic asthma. The anti-IL-5 monoclonal antibody mepolizumab is licensed as an add-on treatment for severe refractory eosinophilic asthma in adults (29), but is not currently recommended by NICE (the appraisal is ongoing).

In the current submission, Teva UK Limited is seeking a recommendation for reslizumab, a monoclonal anti-IL-5 antibody 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. A recent retrospective cohort study of adults in Scotland with severe asthma and at least one estimation of IgE on their records in the preceding two years showed that over half (53.4%) of patients at BTS/SIGN Step 4 or 5 have elevated eosinophil levels and would therefore be eligible for reslizumab therapy (30, 31). A proportion of these patients will also have elevated IgE levels and will therefore alternatively be eligible for omalizumab. The remainder represent a substantial, distinct population of patients who are not eligible for omalizumab therapy (i.e. who are eosinophilic and do not have high IgE levels) for whom there are currently no NICE-

recommended treatment options. Thus, there is a substantial unmet medical need in patients with severe asthma and elevated eosinophils inadequately controlled by ICS for effective, targeted treatment options that reduce exacerbations and improve asthma control and symptoms.

Decision problem addressed in the submission

The objective of this technology appraisal is to evaluate the clinical and cost-effectiveness of reslizumab, in line with its licensed indication, for the treatment of adult patients with severe eosinophilic asthma. The decision problem addressed in this submission is largely in line with the scope issued by NICE (summarised in Table 1).

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from final NICE scope
Population	Adults with asthma with elevated blood eosinophils inadequately controlled by ICS.	As per scope. RCTs comprised: • Pivotal Phase III studies 3082 and 3083: Patients with asthma and elevated blood eosinophils inadequately controlled by medium to high dose ICS • Phase III study 3081: Patients with asthma and elevated blood eosinophils • Supportive Phase III 3084: Patients with moderate to severe asthma	N/A
Intervention	Reslizumab (in addition to best standard care).	As per scope	N/A
Comparator(s)	• BSC without reslizumab • Omalizumab (for people with severe persistent allergic IgE-mediated asthma with elevated blood eosinophils)	• BSC without reslizumab • Omalizumab + BSC for patients who are eligible for either reslizumab or omalizumab (see Section 3.3.2).	N/A
Outcomes	• Asthma control • Incidence of clinically significant exacerbations, including those which require unscheduled contact with healthcare professionals or hospitalisation • Use of OCS	• Asthma control and symptoms • Clinical asthma exacerbations • Lung function • HRQoL • SABA use • Blood eosinophil count • Adverse effects of treatment	Baseline OCS was used by 142 patients in the pivotal reslizumab trials (Studies 3082 and 3083); the dose had to remain stable throughout the trials.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from final NICE scope
	• Patient and clinician evaluation of response • Lung function • Mortality • Time to discontinuation • Adverse effects of treatment • HRQoL		
Economic analysis	The cost-effectiveness of treatments should be expressed in terms of incremental cost per QALY. The time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective.	Markov model to express cost-effectiveness in terms of cost per QALY. The analysis uses a lifetime time horizon. Costs are considered from an NHS and PSS perspective.	Not specified in scope; the economic analysis is aligned to the NICE reference case.
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • People who require maintenance OCS treatment • People who require frequent OCS treatment	The population considered for the base case analysis was adult patients at GINA Steps 4 and 5 who had experienced ≥3 asthma exacerbations in the preceding year. Subgroups considered as part of scenario analyses were: • Adult patients at GINA Step 4/5 who had experienced ≥2 exacerbations • Adult patients at GINA Step 4/5 who had experienced ≥4 exacerbations	Based on clinical experts' advice, the expected treatment effect of reslizumab, and the fact that exacerbations are infrequent events that can vary from one year to the next, patients at GINA Step 4/5 who had experienced ≥3 asthma exacerbations in the preceding year are the appropriate population to receive treatment on the NHS. Sufficient evidence was not available from the reslizumab clinical trials to quantify the impact of treating patients

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from final NICE scope
			with reslizumab on the use of corticosteroids.
Special considerations including issues related to equity or equality	Not specified	Not applicable	N/A

Abbreviations: BSC, best standard of care; HRQoL, health-related quality of life; ICS, inhaled corticosteroids; NHS, National Health Service; OCS, oral corticosteroids; PSS, Personal and Social Services; QALY, quality-adjusted life year; RCT, randomised controlled trial; SABA, short-acting beta-agonist.

1.2 *Description of the technology being appraised*

Reslizumab is a humanised monoclonal antibody (IgG4/κ) against human IL-5 a proinflammatory cytokine that plays a key role in the differentiation, maturation, recruitment and activation of human eosinophils (Summary of Product Characteristics [SmPC], **Error! Reference source not found.**). Reslizumab binds specifically and with high affinity to IL-5, interfering with the binding of IL-5 to eosinophils via its cell surface receptor IL-5Ra ((32) and SmPC, **Error! Reference source not found.**). By neutralising IL-5, reslizumab reduces eosinophil survival and activity; clinical studies have demonstrated that inhibition of IL-5 by reslizumab results in significant reduction of blood and sputum eosinophils (33, 34).

Marketing authorisation from the European Medicines Agency (EMA) is expected in August 2016 (Table 2). The UK launch for reslizumab is planned for [redacted].

Table 2: Technology being appraised

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. • Marketing authorisation: The European Commission Decision is expected 67 days after the CHMP opinion (late 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 (see Section 5.1 of the SmPC [**Error! Reference source not found.**]). 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	Intravenous infusion only. Reslizumab must not be administered

and dosage	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.

Abbreviations: CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; ICS, inhaled corticosteroids; SmPC, summary of product characteristics.

1.3 *Summary of the clinical effectiveness analysis*

Clinical evidence supporting the efficacy and safety of reslizumab for the treatment of patients with asthma and elevated blood eosinophils who are inadequately controlled with medium to high dose ICS comes from four Phase III placebo-controlled randomised controlled trials (RCTs) (the Phase III BREATH programme) and one long-term safety extension study:

- Studies 3082, 3083 and 3081 provide the core efficacy evidence. The 3082 and 3083 trials had an identical design and evaluated reslizumab 3.0 mg/kg administered every 4 weeks over 52 weeks. 3081 evaluated reslizumab 0.3 mg/kg and 3.0 mg/kg administered every 4 weeks over 16 weeks.
- Study 3084 provides supporting evidence for the current submission. This trial assessed the efficacy of reslizumab 3.0 mg/kg, given every 4 weeks for 16 weeks, in relation to baseline blood eosinophil levels in patients with moderate to severe asthma. The subpopulation of patients with a baseline eosinophil level ≥400 cells/μL, the cut-off for the definition of eosinophilic asthma in the reslizumab Phase III confirmatory trials, is relevant for the indication being appraised.
- Study 3085 was an open-label, long-term safety extension of studies 3081, 3082 and 3083.

1.3.1 *Efficacy*

1.3.1.1 Asthma exacerbations

Frequency of clinical asthma exacerbations (CAEs) was the primary endpoint in Study 3082 and Study 3083:

- Both trials met the primary endpoint, with reslizumab leading to a significantly greater reduction in the frequency of adjudicated CAEs during the 52-week treatment period compared with placebo ($p<0.0001$ in both trials).
- All sensitivity analyses of the primary outcome demonstrated a significantly lower CAE frequency with reslizumab versus placebo, supporting the results of the primary analysis.

1.3.1.2 Lung function

Lung function as assessed by forced expiratory volume in one second (FEV_1) was the primary endpoint in Study 3081 and Study 3084, and a secondary endpoint in Studies 3082 and 3083. All four trials showed significant improvements from baseline with reslizumab compared with placebo:

- In Studies 3082 and 3083, significant improvements in FEV_1 were observed with reslizumab versus placebo over 16 weeks of treatment (p<0.0001 and p=0.0037, respectively). Improvements were evident by the first assessment visit (Week 4) and were sustained throughout the 52-week treatment period (nominal p<0.0001 and nominal p=0.0057, respectively, over 52 weeks).
- In Study 3081, both reslizumab doses led to a significantly greater improvement in FEV_1 over 16 weeks, compared with placebo. The treatment effect was greater for the 3.0 mg/kg dose (p=0.0018) than the 0.3 mg/kg dose (p=0.0237), indicating that the higher dose provides the most robust efficacy in this patient population. Sensitivity analyses of the primary outcome supported the results of the primary analysis.
- In Study 3084, there was a significant improvement in FEV_1 at Week 16 (p=0.0436) in patients with a baseline eosinophil level ≥400/µL. No significant treatment effect was observed at Week 16 in patients with baseline eosinophils <400/µL, or in the overall population at Week 16 or over 16 weeks.

1.3.1.3 Asthma control and symptoms

In Studies 3082 and 3083 there were significant improvements from baseline in patient-reported measures of asthma control (Asthma Control Questionnaire [ACQ] score) and asthma symptoms (Asthma Symptom Utility Index [ASUI] score) with reslizumab versus placebo over 16 weeks of treatment. Improvements in these outcomes were evident by the first assessment visit (Week 4) and were sustained throughout the 52-week treatment period.

- In 3082 and 3083, ACQ was significantly improved (decreased) with reslizumab versus placebo over 16 weeks (p=0.0001 and p=0.0032, respectively), and over 52 weeks (nominal p=0.0002 and nominal p=0.0003, respectively). The proportions of patients achieving at least a 0.5-point improvement in ACQ score were greater with reslizumab than with placebo at almost all timepoints. ASUI was significantly improved with reslizumab versus placebo over 16 weeks and over 52 weeks in both trials (3082: p<0.0001 over 16 weeks and nominal p<0.0001 over 52 weeks; 3083: p=0.0037 over 16 weeks and nominal p=0.0011 over 52 weeks).
- In 3081, reslizumab treatment led to significant improvements versus placebo in ACQ and ASUI over 16 weeks; the degree of improvement was generally greater in patients treated with the 3.0 mg/kg dose (p=0.0014 and p=0.0160, respectively) than those given 0.3 mg/kg (p=0.0329 and p=0.0094, respectively).
- In 3084, the effect of reslizumab treatment on improved asthma control tended to increase slightly with increasing baseline blood eosinophil level. The proportion of patients in the overall population who achieved at least a 0.5-point improvement in ACQ score was numerically higher with reslizumab than placebo by Week 4; this treatment effect increased throughout the study, with significant differences seen at Weeks 12 and 16.

1.3.1.4 Quality of life

- In 3082 and 3083, significant improvements from baseline in patient-reported QoL, as assessed by Asthma Quality of Life Questionnaire (AQLQ) score, were observed with reslizumab versus placebo over 16 weeks of treatment (p=0.0143 and p=0.0259, respectively); improvements were evident by the first assessment visit (Week 16) and

were sustained throughout the 52-week treatment period (nominal p=0.0004 and nominal p=0.0052, respectively, over 52 weeks). .

- A significant improvement in QoL was reported with reslizumab 3.0 mg/kg versus placebo in 3081 (p=0.0241); a numerical improvement versus placebo was seen for the reslizumab 0.3 mg/kg dose.

1.3.1.5 Meta-analysis

Meta-analyses of outcomes from the reslizumab Phase II studies 3081, 3082, 3083 and 3084, and the Phase II study Res-5-0010 were conducted (Section 4.9). These analyses showed that there were significantly greater improvements in lung function at 16 and 52 weeks, asthma control at 16 weeks, and QoL at 16 and 52 weeks with reslizumab 3.0 mg/kg compared with placebo. The rates of clinically significant asthma exacerbations were significantly lower with reslizumab versus placebo over the course of the trials. No significant treatment differences in the numbers of patients hospitalised due to exacerbations were identified, although low numbers of these events were reported.

1.3.2 *Safety*

- Reslizumab was generally well tolerated with a safety profile similar to that of placebo (summarised in Section 4.12.3). The most common adverse events (AEs) associated with reslizumab treatment in the RCTs included asthma, nasopharyngitis and upper respiratory tract infection. Across all trials the majority of treatment-emergent AEs (TEAEs) in patients treated with reslizumab were mild or moderate in severity. Serious adverse events (SAEs) were uncommon; the incidence of SAEs in patients who received at least one dose of study drug was slightly lower in those treated with reslizumab 3.0 mg/kg (6%) compared with placebo (9%). One death occurred in the RCTs (placebo group in Study 3082); this was most likely due to accidental combined drug intoxication with fentanyl and diphenhydramine.
- Infusion reactions, administration site reactions, hypersensitivity/anaphylaxis, malignancies, infections, and musculoskeletal/creatine phosphokinase (CPK) abnormalities were designated as AEs of special interest based on potential effects of the anti-IL-5 mechanism of action and on individual study results. Overall, a review of data related to these events did not raise any new safety concerns (Section 4.12.3.2).
- Meta-analyses of safety data from the reslizumab Phase II and III RCTs showed that there were no significant differences between the reslizumab and placebo arms in the proportions of patients discontinuing due to AEs or experiencing SAEs during the trials (see Section 4.9.2).
- The open-label, long-term safety extension Study 3085 (Section 4.12.2) was conducted to obtain additional safety data for reslizumab 3.0 mg/kg. The overall pattern of AEs in this trial was similar to the preceding double-blind studies and no new safety concerns were identified with continuous reslizumab treatment every 4 weeks for up to an additional 24 months.

1.4 *Summary of the cost-effectiveness analysis*

An economic analysis was performed to evaluate the cost-effectiveness of reslizumab as add-on therapy to BSC for the treatment of severe eosinophilic asthma, compared with both BSC alone and with omalizumab as add-on therapy to BSC (for patients with severe

persistent allergic asthma with elevated blood eosinophils). The cost-effectiveness model is a Markov model comprised of six mutually exclusive health states (controlled asthma, uncontrolled asthma, moderate exacerbation, severe exacerbation, all-cause mortality and asthma-related death; see Figure 38). Default analyses use a 60-year (lifetime) time horizon and 3.5% annual discounting of costs and outcomes. Costs are considered from both a National Health Service (NHS) and Personal and Social Services (PSS) perspective.

The patient population considered for the base case analysis is adult patients at GINA Steps 4 and 5 who had experienced at least three exacerbations in the preceding year. Based on clinical experts' advice, the expected treatment effect of reslizumab, and the fact that exacerbations are infrequent events that can vary from one year to the next, this population is believed to be the appropriate population to receive treatment on the NHS. Subgroups according to the number of exacerbations experienced by patients in the year preceding treatment initiation were also considered (see below).

Both the reslizumab and omalizumab arms in the model are subject to a response rule (see Section 5.2.2): patients in the omalizumab arm are assessed for treatment response at 16 weeks into therapy in line with the omalizumab SmPC (35), while response for patients in the reslizumab arm is identified according to an algorithm [redacted]

Cost-effectiveness is reported in terms of incremental cost per quality-adjusted life year (QALY). The base case analysis showed that reslizumab is a cost-effective treatment option compared with both BSC alone and omalizumab, at a willingness-to-pay threshold of £20,000–£30,000 per QALY. The incremental cost-effectiveness ratio (ICER) was estimated to be £24,907 per QALY gained for reslizumab versus BSC (Table 3), and £16,643 per QALY gained for reslizumab versus omalizumab (Table 4). Thus reslizumab as add-on therapy to BSC is a cost-effective use of NHS resources for adult patients with severe eosinophilic asthma who are inadequately controlled despite high-dose ICS plus another medicinal product for maintenance treatment.

Table 3: Base case cost-effectiveness results: Patients with a history of ≥3 exacerbations

Treatment arm	Total			Incremental			ICER/ QALYs, £	ICER / LYG, £
	Costs, £	LYG	QALYs	Costs, £	LYG	QALYs		
BSC	[redacted]	[redacted]	[redacted]					
Reslizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,907	£22,367

Abbreviations: BSC, best standard of care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

Table 4: Base case cost-effectiveness results: Patients with severe persistent allergic IgE-mediated eosinophilic asthma and a history of ≥3 exacerbations

Treatment arm	Total			Incremental			ICER/ QALYs, £ increment	ICER/ QALYs, £ vs BSC
	Costs, £	LY	QALYs	Costs, £	LYG	QALYs		

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]	£33,254	£33,254
Reslizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,643	£24,907

Abbreviations: BSC, best standard of care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

The cost-effectiveness findings were robust to changes in input parameters and deterministic analyses supported the likelihood that reslizumab is a cost-effective treatment option.

A probabilistic sensitivity analysis (PSA) was conducted using a conservative approach: uniform distributions were used when limited data were available, including on one of the main driver of results: the rate of exacerbations in the BSC arm. In addition, given the model structure, transition probabilities were drawn independently for reslizumab and BSC, rather than drawing the relative treatment effect, thereby leading to higher levels of uncertainty.

From this PSA (1000 iterations), the probability of reslizumab being cost-effective versus BSC alone was estimated to be 41.8% at a £30,000 threshold and the probability of reslizumab being cost-effective versus omalizumab was estimated to be 38.6% at the same threshold.

Cost-effectiveness was also estimated for patient subgroups according to the number of exacerbations in the preceding year: In adults at GINA Step 4/5 who had experienced at least two exacerbations, the ICER was estimated to be £33,774 per QALY gained for reslizumab versus BSC, while in adults at GINA Step 4/5 who had experienced at least four exacerbations, the ICER was lower at £20,006/QALY.

2 The technology

2.1 *Description of the technology*

Brand name: CINQAERO

UK approved name: Reslizumab

Therapeutic class: Drugs for obstructive airway diseases, other systemic drugs for obstructive airway diseases (ATC code: R03DX08)

Mechanism of action: Reslizumab is a humanised monoclonal antibody (IgG4/κ) against human interleukin-5 (IL-5), a proinflammatory cytokine that plays a key role in the differentiation, maturation, recruitment and activation of human eosinophils (Summary of Product Characteristics [SmPC], **Error! Reference source not found.**). Reslizumab binds specifically and with high affinity to IL-5, interfering with the binding of IL-5 to eosinophils via its cell surface receptor IL-5Ra ((32) and SmPC, **Error! Reference source not found.**). By neutralising IL-5, reslizumab reduces eosinophil survival and activity; clinical studies have demonstrated that inhibition of IL-5 by reslizumab results in significant reduction of blood and sputum eosinophils (33, 34).

No formal clinical drug interaction studies have been performed with reslizumab; however, based on the characteristics of reslizumab, drug-drug interactions (DDIs) are not expected. Based on population pharmacokinetic analyses, systemic exposure to reslizumab appears to be unaffected by circulating anti-reslizumab antibodies. Concomitant use of either leukotriene antagonists or systemic corticosteroids does not affect the pharmacokinetics of reslizumab (SmPC, **Error! Reference source not found.**).

2.2 *Marketing authorisation/CE marking and health technology assessment*

2.2.1 *Marketing authorisation/CE marking*

For the indication considered in this submission:

- Regulatory submission to the European Medicines Agency (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.
- Marketing authorisation: The European Commission Decision is expected 67 days after the CHMP opinion (late August 2016).

2.2.2 *(Anticipated) indication(s) in the UK*

Reslizumab is indicated as add-on therapy in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment. No additional indications for reslizumab are anticipated at the time of this submission.

2.2.3 *(Anticipated) restrictions or contraindications*

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

The special warnings and precautions for use listed in the SmPC (**Error! Reference source not found.**) are:

- General:
  - Asthma-related symptoms or exacerbations may occur during treatment.
  - Reslizumab should not be used to treat acute asthma exacerbations. Patients should be instructed to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment.
- Acute systemic reactions (including anaphylactic reactions):
  - Anaphylactic reactions have been reported in association with reslizumab (0.2% of patients; see Section 4.8 of the SmPC).
  - Patients should be monitored during and for an appropriate time after administration of reslizumab. If an anaphylactic reaction occurs, administration of reslizumab should be stopped immediately and appropriate medical treatment should be provided; reslizumab must be discontinued permanently.
- Parasitic (helminth) infections:
  - Eosinophils may be involved in the immunological response to some helminth infections.
  - Patients with pre-existing helminth infections should be treated before starting reslizumab therapy. If patients become infected while receiving treatment with reslizumab and do not respond to anti-helminth treatment, temporary discontinuation of therapy should be considered.
- Paediatric population:
  - The safety and efficacy of reslizumab in children and adolescents aged up to 17 years have not been established for the indication of CINQAERO. No data are available for children aged up to 11 years.
- Excipients with known effect:
  - Each 100 mg vial contains 0.20 mmol (4.6 mg) of sodium, i.e. it is essentially ‘sodium free’.

2.2.4 *SmPC/Information for use and (Draft) assessment report*

The SmPC is provided in **Error! Reference source not found.**. The reslizumab European public assessment report (EPAR) is not yet available; however the CHMP Day 180 List of Questions and manufacturer responses are provided in **Error! Reference source not found.**.

2.2.5 *Main issues discussed by regulatory authorities*

The main points relating to efficacy and safety that were raised in the CHMP Day 180 questions are summarised below:

Clinical efficacy – reslizumab indication

The CHMP highlighted that it should be clear in the indication that the target population is patients who are inadequately controlled despite high-dose inhaled corticosteroids (ICS) plus another controller, and that the indication should therefore be revised from *'CINQAERO is indicated as add-on treatment in adult patients with severe eosinophilic asthma'* to *'CINQAERO is indicated as add-on therapy in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose ICS plus another controller'*.

Teva UK Limited accepted the proposed indication, responding that, while reslizumab was observed to be effective across the spectrum of Global Initiative for Asthma (GINA) Step 4 and Step 5 patients, it understands the need to better define the positioning of the product in the asthma treatment paradigm. The stepwise approach to treatment recommended in the British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) guidelines is in line with the GINA guidelines (22).

Teva UK Limited proposed however to maintain Section 5.1 of the Common Technical Document in line with the efficacy results in the proposed SmPC that was submitted with the responses to the D180 List of Questions for the following reasons:

- GINA Step 4 includes patients on both medium- and high-dose ICS plus another controller, and these patients represent broadly overlapping populations. There is limited benefit of increasing ICS to high doses in general, with increased risk of adverse corticosteroid effects, and thus it is recommended that high-dose ICS are used on a temporary basis. This gives healthcare professionals the possibility to step ICS levels up and down depending on the patient's current level of control.
- Reslizumab has a robust efficacy profile across the spectrum of GINA Step 4 and Step 5 patients, including the major GINA Step 4 subgroups of medium- and high-dose ICS plus another controller. The magnitude and consistency of the efficacy across GINA Steps 4/5 and GINA Step 4 patients with elevated eosinophils supports the benefit of reslizumab in this population.

On 23 June 2016 the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for reslizumab. The full indication was revised to: '*CINQAERO 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*'.

Clinical safety – further clarification on AEs

The CHMP requested further clarification on:

- the higher number of patients with blood creatine phosphokinase elevations described in the Integrated Summary of Safety compared with the Response to D120 List of Questions

- how the 'events that were reported in <1% of patients in the reslizumab 3.0 mg/kg treatment group and more frequently than in the placebo group' is applied to all adverse events (AEs)
- why treatment-related AEs, of which the number of patients is higher in the reslizumab group than in the placebo group, is not included in Section 4.8 of the SmPC.

Teva UK Limited provided the required clarification on these points and included further data on AEs in its response to the Day 180 questions.

2.2.6 *Anticipated date of availability in the UK*

The UK launch for reslizumab is planned for [redacted].

2.2.7 *Regulatory approval outside the UK*

Regulatory approval of reslizumab outside the UK is shown in Table 5.

Table 5: Regulatory approval of reslizumab outside the UK

Indication	Locations
Reslizumab is indicated as add-on treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose ICS plus another medicinal product for maintenance treatment.	28 EU members states and the EEA countries Iceland, Liechtenstein and Norway (via the EMA centralised authorisation procedure; marketing authorisation expected in August 2016 [see Section 2.2.1])
Reslizumab is indicated for add-on maintenance treatment of patients with severe asthma aged 18 years and older, and with an eosinophilic phenotype.	US (via FDA approval). The Pulmonary-Allergy Drugs Advisory Committee recommended approval of reslizumab on 10 December 2015. Reslizumab was approved by the FDA on 23 March 2016 and launched in the US in April 2016.

Abbreviations: EEA, European Economic Area; EU, European Union; FDA, US Food and Drug Administration; ICS, inhaled corticosteroid; US, United States.

2.2.8 *Ongoing HTAs in the rest of the UK*

A submission to the Scottish Medicines Consortium (SMC) is currently planned for [redacted]. A submission to the All Wales Medicines Strategy Group (AWMSG) is not currently planned while the NICE appraisal process is ongoing.

2.3 *Administration and costs of the technology*

Information concerning administration and costs of the technology is presented in Table 6.

Table 6: Costs of the technology being appraised

	Information	Source
Pharmaceutical formulation	Concentrate for solution for infusion (sterile concentrate). Clear to slightly hazy opalescent, colourless to slightly yellow solution with pH 5.5. Proteinaceous particles might be present.	SmPC (**Error! Reference source not found.**)

	Information	Source
Acquisition cost (excluding VAT)	Anticipated reslizumab list price: • £499.99 (100 mg vial) • £124.99 (25 mg vial) Anticipated PAS price: • £[redacted] (100 mg vial) • £[redacted] (25 mg vial)	Data on file
Method of administration	Intravenous infusion only. Reslizumab must not be administered by the subcutaneous, oral or intramuscular route. The appropriate volume of reslizumab should be dispensed into an infusion bag containing 50 mL sodium chloride 9 mg/mL (0.9%) solution for infusion. The volume (in mL) required from the vial(s) should be calculated as follows: 0.3 x patient body weight (in kg). The diluted medicinal product should then be administered as a 20–50 minute intravenous infusion.	SmPC (**Error! Reference source not found.**)
Doses	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).	SmPC (**Error! Reference source not found.**)
Dosing frequency	The recommended dose of reslizumab, based on body weight, is 3.0 mg/kg, given once every four weeks.	SmPC (**Error! Reference source not found.**)
Average length of a course of treatment	Reslizumab is intended for long-term treatment. A decision to continue therapy is based on disease severity and level of exacerbation control.	SmPC (**Error! Reference source not found.**)
Average cost of a course of treatment	[redacted]	Cost-effectiveness model (Section 5.6.1) and SmPC (**Error! Reference source not found.**)
Anticipated average interval between courses of treatments	N/A. None specified in the SmPC	SmPC (**Error! Reference source not found.**)
Anticipated number of repeat courses of treatments	N/A. There is no reference to repeat courses in the SmPC	SmPC (**Error! Reference**

	Information	Source
		source not found.)
Dose adjustments	N/A. No dose adjustments are recommended in the SmPC. 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.	SmPC (**Error! Reference source not found.**)
Anticipated care setting	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 should be administered intravenously by a healthcare professional. The patient should observed over the duration of the infusion and for an appropriate period of time afterwards.	SmPC (**Error! Reference source not found.**)

Abbreviations: N/A, not applicable; SmPC, summary of product characteristics.

2.3.1 *Patient access scheme*

A simple patient access scheme (PAS) has been submitted to PASLU and the Department of Health and is currently under review.

2.4 *Changes in service provision and management*

2.4.1 *Additional test/investigations*

No additional tests or investigations are required to identify the population for whom reslizumab is indicated beyond those that are already part of current clinical practice. A blood test for eosinophil levels is already performed during the screening of patients for severe asthma. Therefore, it is anticipated that no additional NHS resources will be required.

2.4.2 *Main resource use to the NHS associated with the technology*

It is anticipated that reslizumab will be initiated and monitored in specialist centres. Reslizumab should be administered intravenously by a healthcare professional prepared to manage hypersensitivity reactions including anaphylaxis. The appropriate volume of reslizumab should be dispensed into an infusion bag containing 50 mL sodium chloride 9 mg/mL (0.9%) solution for infusion. The volume (in mL) required from the vial(s) should be calculated as follows: 0.3 x patient body weight (in kg). The diluted medicinal product should then be administered as a 20–50 minute intravenous infusion using a 0.2 µm in-line filter.

It is expected that severe asthma will remain centrally commissioned under NHS England at the time of reslizumab launch.

2.4.3 *Additional infrastructure requirements*

Not applicable.

2.4.4 *Patient monitoring requirements*

Monitoring requirements directly following administration of reslizumab will be driven by locally-led protocols. Patients should be monitored over the duration of the infusion and for an appropriate period of time afterwards; there is no time period specified in the draft SmPC. Patients were monitored for an appropriate length of time following administration in the clinical trials. Protocols for patient monitoring post-administration of omalizumab already exist, although capacity may need to be addressed to meet the increased demand from reslizumab patients.

2.4.5 *Need for concomitant therapies*

Not applicable.

2.5 *Innovation*

As described in more detail in Section 3, reslizumab represents a significant advance in the management of severe asthma:

- It is become increasingly recognised that asthma is a heterogeneous disease made up of different phenotypes; eosinophilic asthma is a well-recognised phenotype of severe asthma (1).
- No treatments are currently recommended by NICE for treating patients with eosinophilic (IL-5-mediated) asthma.
    - As described in Section 3.3.2, a proportion of the reslizumab-eligible population will have elevated IgE levels in addition to elevated eosinophils and will therefore also be eligible for treatment with the anti-IgE monoclonal antibody omalizumab (Xolair). Omalizumab is recommended by NICE for treating severe persistent allergic asthma as an add-on treatment option in patients aged six years and older who need continuous or frequent treatment with oral corticosteroids (OCS) (24, 28).
    - However, there also remains a substantial, distinct population of patients who are not eligible for omalizumab (i.e. who are eosinophilic and do not have high IgE levels) for whom there are currently no recommended treatment options.
    - The anti-IL-5 monoclonal antibody mepolizumab is licensed as an add-on treatment for severe refractory eosinophilic asthma in adults (29), but is not currently recommended by NICE (appraisal ongoing).
- Reslizumab binds specifically and with high affinity to IL-5, interfering with the binding of IL-5 to eosinophils and thus reducing eosinophil maturation, survival and activity ((32) and SmPC, **Error! Reference source not found.**). No other targeted, biologic therapies with this novel mechanism of action are currently recommended.

Reslizumab addresses a clear unmet medical need for effective, targeted treatment options in patients with severe asthma and elevated eosinophils inadequately controlled with high-dose ICS plus another medicinal product for maintenance treatment (see Section 3.7):

- 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 (9, 22).

- Long-term use of corticosteroids is associated with several well-known adverse effects (23-27), and corticosteroid insensitivity is a feature of severe asthma (36-39).
- Elevated eosinophils are associated with an increased frequency of asthma exacerbations and poor disease control (see Section 3.2.1).
- Asthma exacerbations are a prominent feature of poorly-controlled, severe asthma (11, 12).

Results from the pivotal Phase III trials, presented in Section 4 of the current submission, demonstrate that reslizumab significantly reduces (approximately halves) the frequency of clinical asthma exacerbations (CAEs), significantly improves lung function, asthma control and symptoms, and health-related quality of life (HRQoL), and is well tolerated, in patients with asthma and elevated blood eosinophils inadequately controlled with ICS.

3 Health condition and position of the technology in the treatment pathway

3.1 *Disease overview*

3.1.1 *Asthma disease classification*

Asthma is a common, chronic respiratory disease characterised by reversible airflow obstruction, bronchial hyperresponsiveness and airway inflammation (1). Symptoms vary in frequency and severity and include wheezing, breathlessness, chest tightness, sputum production and coughing. These symptoms can have many triggers, including environmental factors such as allergen or irritant exposure, pollution and changes in the weather, and those related to the individual patient such as exercise, viral respiratory infections, hormonal changes and stress (9, 40). Asthma symptoms characteristically vary over time and individuals may be symptom free for weeks or months at a time. Conversely, patients can experience episodic 'exacerbations', which represent an acute or subacute flare-up in symptoms and decrease in lung function compared with the patient's usual status. Severe exacerbations are potentially life threatening and require prompt treatment and close monitoring (9).

The severity of an individual patient's asthma may change over months or years. Asthma severity should be assessed retrospectively from the level of treatment required to control symptoms and exacerbations, once the patient has been on regular controller treatment for several months (8, 9). The current BTS/SIGN British guideline for the management of asthma (22) doesn't provide standard definitions of the type, severity or frequency of asthma symptoms; however, as detailed in Section 3.3.1, it recommends a stepwise approach to treatment based on the initial severity of patients' disease. In its 2016 report, Global Strategy for Asthma Management and Prevention (9), GINA defines severe asthma as 'asthma that requires Step 4 or 5 treatment, e.g. high-dose inhaled corticosteroid/long-acting beta-agonist (ICS/LABA), to prevent it from becoming uncontrolled, or asthma that remains uncontrolled despite this treatment' (Table 7; see Section 3.3.1 for a description of the recommended treatment steps). Similarly, the European Respiratory Society/American Thoracic Society (ERS/ATS) Task Force (8) defines severe asthma as 'asthma that requires treatment with high-dose ICS plus a second controller and/or systemic corticosteroids to prevent it from becoming uncontrolled, or that remains uncontrolled despite this therapy'. Fulfilment of this definition predicts a high degree of future risk both from the disease itself (exacerbations and loss of lung function), and from side-effects of medications (8).

Table 7: GINA definition of asthma severity

Severity	Description
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

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

3.1.2 *Role of eosinophils in severe asthma*

It is increasingly evident that severe asthma is not a single disease, given the variety of clinical presentations, physiological characteristics and outcomes. To aid understanding of this heterogeneity, recognisable clusters of demographic, clinical and/or pathophysiological characteristics have been identified. These 'phenotypes' result from complex interactions between genetic and environmental factors (8, 9).

Eosinophilic asthma is a well-recognised phenotype of severe asthma that is associated with elevated levels of eosinophils in the tissue and sputum, and a thickening of the basement membrane (1). Eosinophils are a type of bone marrow-derived white blood cell that has long been recognised to play a major role in airway inflammation in asthma (10). They are classically associated with allergic sensitisation and are part of the inflammatory response dominated by T-cells, a type of white blood cell involved in the immune response (1). In asthma, two pathways, driven by either allergen-specific T helper type 2 (Th2) cells or allergen-independent group 2 innate lymphoid cells (ILC2) lead to the production of IL-5, which subsequently induces eosinophilic airway inflammation via its effect on eosinophil differentiation, migration and activation (41).

Elevated eosinophils are associated with an increased frequency of asthma exacerbations and poor disease control (see Section 3.2.1) and hence there is a need for accurate phenotype identification and targeted treatments in patients with severe eosinophilic asthma. Measurement of eosinophils in induced sputum is a sensitive and reliable biomarker for identifying eosinophilic inflammation in asthma; however this measurement is not widely used in the clinical setting as it requires technical expertise and may cause patient discomfort. Blood eosinophil counts, which are more practical to obtain, have been shown to correlate closely with sputum eosinophil levels and can therefore be used to facilitate individualised treatment and improved asthma management (14, 42-44). Fowler et al (44) showed that increasing the blood eosinophil cut-off value increases the positive predictive value for sputum eosinophils ≥ 2%, with cut-offs of ≥150, ≥300 and ≥450 cells/μL having predictive values of 45.2%, 65.6% and 89.2%, respectively. In another study, Wagener et al (43) aimed to quantify the relationship between blood eosinophil counts and sputum eosinophilia. Using a blood eosinophil cut-off of ≥270 cells/μL, the authors reported a diagnostic accuracy of 89% ($p<0.001$) for the correlation with sputum eosinophils ≥3%, and 88% ($p<0.001$) for the correlation with sputum eosinophils ≥2%.

3.1.3 *Epidemiology*

Asthma is one of the most common chronic conditions worldwide. In Europe, asthma affects approximately 30 million children and adults under the age of 45. In most European countries, the prevalence of the disease increased substantially between 1950 and 2000 but, at least in Western countries, this increase has levelled off over the last decade. The prevalence of asthma tends to be higher in northern and western countries, where over 10% of the population aged 18–44 years may be affected (2).

The number of people affected by asthma in the UK is among the highest in the world; according to the British Lung Foundation and Asthma UK, 8 million people (over 12% of the UK population) have been diagnosed with asthma and around 5.4 million people are currently receiving treatment for the disease: 4.3 million (1 in 12) adults and 1.1 million

(1 in 11) children (3, 4). Asthma accounts for high numbers of consultations in primary care, out-of-hours services and hospital emergency departments; during 2011–2, there were over 65,000 hospital admissions for asthma in the UK (19).

The prevalence of severe asthma in adults or children is not well understood, likely due to difficulty in estimating these figures due to disease heterogeneity. However, the proportion is often estimated to be 5–10% of the total asthma population (8). While the exact prevalence of eosinophilic asthma is not known, a recent study in patients with difficult-to-treat asthma receiving high-dose inhaled and/or oral corticosteroids showed that 32% (14 out of 44 patients) exhibited permanent sputum eosinophilia, defined as sputum eosinophils ≥2% at baseline and at a 5-year follow up (45).

3.2 *Burden to patients, carers and society*

3.2.1 *Clinical burden*

Asthma exacerbations, which usually occur as a result of an inflammatory response to environmental and occupational allergens, exposure to viruses, or in response to exercise or stress, lead to morbidity in asthma and can be fatal. Exacerbations are a prominent feature of poorly-controlled, severe asthma and are thought to be the primary cause of the estimated 250,000 annual asthma-related hospital admissions in the European Union (EU) (11, 12). The ERS/ATS task force defines severe asthma exacerbations as events that require urgent action by the patient and physician to prevent a serious outcome such as hospitalisation or death, and defines moderate asthma exacerbations as troublesome events that prompt a change in treatment but are not severe (46). In the BTS/SIGN guideline, ‘acute, severe asthma’ is defined as that which meets any of the following criteria on initial assessment: peak expiratory flow 33–50% best or predicted; respiratory rate ≥25/minute; heart rate ≥110/minute; or the inability to complete sentences in one breath (22, 47). Risk factors for exacerbations, independent of symptom control, include having ≥1 exacerbation in the previous year, blood eosinophilia, impaired lung function, poor adherence to treatment, incorrect inhaler technique, and smoking (9).

The association of elevated eosinophil levels with both exacerbations and with acute respiratory events (defined more broadly as an asthma-related hospital attendance/ admission, emergency department visit, prescription for acute OCS, or prescription for antibiotics in conjunction with an asthma-related primary care consultation) is supported by several studies (13-15), and eosinophils have been found to be a major risk factor for frequent exacerbations (12, 16, 17). A recent study (17) reported that elevated blood eosinophil counts (>400 cells/µL) are the single best predictor of multiple exacerbations among all of the demographic and clinical indices examined. A blood eosinophil count >400 cells/µL significantly increased the likelihood of two or more exacerbations by more than 1.4-fold compared with those with lower eosinophil counts (<400 cells/µL; $p<0.001$).

When asthma is controlled, severe exacerbations are rare and episodes such as daytime asthma symptoms, night waking due to asthma, reliever use and activity limitation due to asthma occur infrequently (9). Several studies have demonstrated an association between inflammation (particularly eosinophilic inflammation) and asthma control (48-50); in a recent historical UK cohort study, patients with blood eosinophil levels

>400 cells/µL had significantly lower odds of achieving overall asthma control, compared with patients with blood eosinophils ≤400 cells/µL (37.2% and 43.0% of patients, respectively, achieved control; odds ratio (OR)=0.74) (14).

3.2.2 *Impact on quality of life*

Asthma can have a considerable negative impact on patients' HRQoL and can affect many areas of everyday life, including work, exercise and travel. The main factors affecting HRQoL are physical symptoms leading to a reduction in the ability to carry out physical activity, and psychological effects leading to fear of symptoms and exacerbations, worries about the availability of appropriate medications, and the avoidance of environmental risk factors (51).

Lack of disease control is frequently reported to increase the negative impact of asthma on HRQoL, compared with well-controlled disease (52-55). An analysis of the 2010 European National Health and Wellness Survey (NHWS) found that people with well-controlled asthma rate their overall HRQoL better than those with poorly-controlled disease (52); patients with well-controlled asthma scored significantly higher than those with poorly-controlled asthma on both the physical and mental component scores of the SF-12 (48.0 vs 39.9, and 45.0 vs 40.6, respectively; p<0.001 for both). HRQoL has also been shown to deteriorate with increasing asthma severity. A UK study using the Juniper Mini Asthma Quality of Life Questionnaire (AQLQ-J) showed that adult patients with severe asthma score lower (indicating reduced functional and psychological wellbeing) compared with those with milder symptoms (56).

Poor asthma control also has a substantial negative impact on work productivity for employed patients. The 2010 European NHWS reported increased absenteeism (10.4% vs 7.0%; p=0.01), impairment while at work due to health (32.5% vs 18.0%; p<0.001) and activity impairment due to health (48.8% vs 26.4%; p<0.001) in people with poorly controlled asthma compared with those whose asthma was well controlled (52).

3.2.3 *Economic burden*

The management of asthma and the treatment of associated comorbidities imposes a substantial burden on national healthcare systems, with patients likely to be long-term users of healthcare resources. Poor disease control is associated with greater use of healthcare resources; patients with poorly-controlled asthma require more visits to healthcare professionals (HCPs; including GPs and respiratory specialists), more visits to emergency departments, and are hospitalised more often, than those with well-controlled asthma (52, 53). The economic burden of asthma increases with greater disease severity (57-59). Poor asthma control is also associated with increased costs (52, 60-62), typically arising from the management of exacerbations.

The economic costs associated with asthma are estimated to rank as one of the highest among chronic diseases. The total cost of asthma in Europe is estimated at €33.9 billion (based on 2011 values for EU countries), with €19.5 billion attributable to direct costs (medicine, inpatient and outpatient care), and the remaining €14.4 billion due to indirect costs (lost productivity due to work absence and early retirement) (5). The economic burden of asthma in the UK is substantial. Studies on the epidemiology and burden of

allergy reported direct healthcare expenditure, driven mainly by asthma, of over £1 billion in England and Wales, and over £130 million in Scotland (6, 7).

3.3 *Clinical pathway of care*

3.3.1 *Management of asthma*

The overall aim of asthma management is to achieve good disease control with minimal future risk of symptoms and side effects of treatment, and with patients able to lead a normal, active life (9, 22). This should be achieved through both individualised treatment and through patients developing an understanding of what provokes their symptoms so that these triggers can be avoided (63). In the BTS/SIGN British guideline for the management of asthma (22), complete disease control is defined as:

- No daytime symptoms
- No night time awakening due to asthma
- No need for rescue medication
- No asthma attacks
- No exacerbations
- No limitations on activity including exercise
- Normal lung function (in practical terms, forced expiratory volume in one second [FEV_1] and/or peak expiratory flow [PEF] >80% predicted or best)
- Minimal side effects from medication

The BTS/SIGN guideline (22) recommends a stepwise approach to treatment in adults. Patients should start treatment at the step most appropriate to the initial severity of their asthma, and aim to maintain asthma control by stepping up treatment when necessary and stepping down when control is good. The recommended steps are summarised in Table 8.

Table 8: BTS/SIGN recommended stepwise approach to treatment in adults

Step	Treatment
Step 1: Mild intermittent asthma	Inhaled SABA as required
Step 2: Regular preventer therapy	Add ICS 200–800 µg/day† (starting dose should be appropriate to severity of disease; 400 µg is appropriate for many patients)
Step 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.
Step 4: Persistent poor control	Consider increasing the dose of ICS up to 2000 µg/day; consider adding a fourth drug (e.g. LTRA, slow-release theophylline or β_2 agonist tablet).

Step	Treatment
Step 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.

Abbreviations: BTS, British Thoracic Society; ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; LTRA, leukotriene receptor antagonist; SABA, short-acting beta-agonist; SIGN, Scottish Intercollegiate Guidelines Network.
[†]Beclometasone dipropionate (BDP) or equivalent.

Specific recommendations for the management of the population relevant to the current submission – defined in the NICE scope as adults with asthma and elevated blood eosinophils inadequately controlled by ICS – are limited. However, as described in Section 3.1.1, this population comes under the both the ERS/ATS Task Force (8) and GINA (9) definitions of severe asthma. In line with the BTS/SIGN guidelines, GINA recommends a stepwise treatment approach to control asthma symptoms and minimise future risk (Table 9) (9). GINA defines three main categories of pharmacological options for the long-term treatment of asthma:

- Controller medications (used for regular maintenance treatment). These reduce airway inflammation, control symptoms, and reduce future risks such as exacerbations and decline in lung function. Regular daily controller treatment should be initiated as soon as possible after a diagnosis of asthma is made.
- Reliever (rescue) medications: These are provided to all patients for as-needed relief of breakthrough symptoms, including during worsening asthma or exacerbations. They are also recommended for short-term prevention of exercise-induced bronchoconstriction. Reducing, and ideally eliminating, the need for reliever treatment is an important goal in asthma management and a measure of treatment success.
- Add-on therapies (for patients with severe asthma): These may be considered when patients have persistent symptoms and/or exacerbations despite optimised treatment with high dose controller medications (usually a high dose ICS and a LABA) and treatment of modifiable risk factors.

After commencement of treatment, ongoing decisions are based on a cycle of assessment, treatment adjustment, and review of the response. However, there is currently not clear guidance on the assessment of outcomes and [redacted]

Asthma controller medication should be adjusted up or down to achieve good symptom control and minimise risk of future exacerbations, fixed airflow limitation and medication side-effects. Once good asthma control has been maintained for 2–3 months, treatment may be stepped down in order to find the patient's minimum effective treatment. If symptoms and/or exacerbations persist despite 2–3 months of controller treatment, the

following should be assessed and corrected before stepping up treatment: 1) incorrect inhaler technique; 2) poor adherence; 3) persistent exposure to allergens, tobacco smoke, air pollution or medications such as beta-blockers (or, in some patients, non-steroidal anti-inflammatory drugs [NSAIDs]); 4) comorbidities that may contribute to respiratory symptoms and poor quality of life (QoL); and 5) incorrect diagnosis. Patients should also receive guided self-management education (self-monitoring, a written action plan and regular review) and advice about non-pharmacological therapies such as physical activity, weight loss and avoidance of sensitisers. Modifiable risk factors and comorbidities such as smoking, obesity and anxiety should be treated (9).

Table 9: GINA recommended stepwise approach to treatment

Step	Treatment		
	Preferred controller	**Other controller options**	**Reliever**
Step 1		Consider low dose ICS	SABA as needed
Step 2	Low dose ICS	• LTRA • Low dose theophylline†	
Step 3	Low dose ICS/LABA‡	• Medium/high dose ICS • Low dose ICS + LTRA (or + theophylline†)	SABA as needed or low dose ICS/formoterol§
Step 4	Medium/high dose ICS/LABA	• Add tiotropium†¶ • High dose ICS + LTRA (or + theophylline†)	
Step 5	Refer for add-on treatment (e.g. tiotropium, omalizumab, mepolizumab)	Add low dose OCS	

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; SABA, short-acting beta-agonist.
†Not for children aged <12 years. ‡For children aged 6–11 years, the preferred Step 3 treatment is medium dose ICS. §Low dose ICS/formoterol is the reliever medication for patients prescribed low dose budesonide/formoterol or low dose beclometasone/formoterol maintenance and reliever therapy.
¶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.

Thus, in accordance with the guidelines summarised above, the population relevant to the current submission – adults with asthma and elevated blood eosinophils inadequately controlled by ICS – is equivalent to patients at Step 4 and/or Step 5 of the BTS/SIGN and GINA treatment pathways. BSC for these patients is high dose ICS in combination with other controller medications, with or without OCS. However, as described in more detail in Section 3.7, there are several well-known adverse effects of long-term corticosteroid use and guidelines recommend that corticosteroids are administered at the lowest possible dose (22, 65, 66).

In recent years the focus of severe asthma management has shifted towards individualised care and phenotype-targeted biological therapies (8). The anti-IgE monoclonal antibody omalizumab (Xolair) is recommended for treating severe persistent allergic asthma as an add-on treatment option in patients aged six years and older who need continuous or frequent treatment with OCS (24, 28). The anti-IL-5 monoclonal antibody mepolizumab is licensed as an add-on treatment for severe refractory

eosinophilic asthma in adults (29), but is not currently recommended by NICE (appraisal ongoing).

3.3.2 *Positioning of reslizumab*

Reslizumab is indicated as add-on treatment to BSC in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment (SmPC, **Error! Reference source not found.**). Thus, patients eligible for reslizumab will be at Step 4 and/or Step 5 of the BTS/SIGN and GINA treatment guidelines (see Section 3.3.1).

In the current submission, the primary positioning of reslizumab within the asthma care pathway is therefore for patients who are:

- aged 18 or older with severe asthma (GINA step 4/5);
- with elevated eosinophils (blood eosinophil level ≥400 cells/µL).

A recent retrospective cohort study of adults with severe asthma in Scotland showed that over half (53.4%) of patients at BTS/SIGN Step 4 or 5 are eosinophilic, defined as a blood eosinophil count ≥400 cells/µL, and would therefore be eligible for treatment with reslizumab (30, 31). A proportion of these patients will have elevated IgE levels in addition to elevated eosinophils and will therefore alternatively be eligible for omalizumab therapy. However, there also remains a substantial, distinct population of patients who are not eligible for omalizumab therapy (i.e. who are eosinophilic and do not have high IgE levels) for whom there are currently no NICE-recommended treatment options.

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

- BSC without reslizumab (for patients with an eosinophilic phenotype who are not eligible for omalizumab)
- Omalizumab + BSC (for patients in the 'overlap' population – i.e. those exhibiting both an eosinophilic [IL-5-mediated] and an IgE-mediated phenotype)

3.4 *Life expectancy*

Although asthma is generally considered to have a low mortality risk compared with other chronic diseases (such as cardiovascular disease), it remains a potentially life-threatening condition. In 2007 the World Health Organization estimated that there were 250,000 asthma-related deaths per year (67). According to the Global Burden of Disease Study, the number of deaths globally due to asthma in 2010 was more than 345,000 (68). The number of reported asthma deaths in the UK remains among the highest in Europe (19). Office for National Statistics and National Records for Scotland data show that in 2014 there were a total of 1133 deaths in England, Wales and Scotland where the underlying cause was asthma (69, 70).

In an analysis of asthma mortality rates in UK patients hospitalised for asthma from 2000–2005, the total number of deaths during the 5-year period was 1063 patients from 250,043 hospital admissions (0.43%). The highest proportion of deaths following asthma admission was observed in patients aged ≥45 years (798 out of 67,060 patients; 1.19%).

For admissions for acute severe asthma (ICD-10 code J46), 226 out of 26,340 (0.86%) patients died (20). A more recent study of mortality rates for adults in Scotland following hospitalisation for asthma from 1981–2009 identified 1000 case fatalities within 30 days of admission from 116,457 asthma admissions during the study period (0.86%). The likelihood of death increased with increasing age group, with the majority (>60%) of fatalities occurring in those aged ≥65 years (21).

The 2014 National Review of Asthma Deaths, conducted to investigate the circumstances surrounding asthma deaths in the UK, analysed data on 195 deaths from February 2012–January 2013 that were thought to be due to asthma. Of the 155 patients for whom asthma severity could be estimated, 61 (39%) appeared to have severe asthma, (defined as those who were prescribed four asthma medications and those who had been admitted to hospital in the past year, needed daily OCS or had two or more prescriptions for systemic corticosteroids in the past year) (19).

3.5 *Relevant NICE guidance, pathways or commissioning guides*

The NICE clinical guideline 'Asthma management' is currently being developed and is due to be published in June 2017. This guideline will cover adults, children and young people with a diagnosis of asthma, and will give special consideration to subgroups based on age (currently proposed to be children under 5 years, children aged 5–16 years, and adults and young people aged over 16 years). The NICE final scope for this guidance states that it will not cover 'Biologics (for example Omalizumab)' and thus it is also not expected to cover the anti-IL-5 antibodies reslizumab and mepolizumab (71). The recommendations within this guideline will be added to the 'management' section of the NICE asthma pathway (28).

No NICE guidance for management in the specific population relevant to this submission has been published. However, other relevant NICE guidance documents are:

- TA278: Omalizumab for treating severe persistent allergic asthma (24)
  - Omalizumab is recommended as an add-on treatment option for patients aged six years and older with severe persistent allergic asthma who need continuous or frequent treatment with OCS (see Section 3.3)
  - This guidance was used to create the management of 'Difficult or severe asthma' section of the NICE asthma pathway
- TA138: Inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over (65)
  - This guidance was used to create the 'Inhaled corticosteroid' section of the NICE asthma pathway
- KTT5: High-dose inhaled corticosteroids in asthma (66)

NICE has also published the Asthma Quality Standard (QS25), which covers the diagnosis and treatment of asthma in adults, young people and children aged 12 months and older (63). This standard includes a quality statement on 'difficult asthma', defined as asthma with symptoms despite treatment at Steps 4 or 5 of the BTS/SIGN guideline plus one of the following: 1) an event of acute severe asthma which is life threatening, requiring invasive ventilation within the last 10 years; 2) requirement for maintenance

oral steroids for at least 6 months at a dose ≥7.5 mg prednisolone per day or a daily dose equivalent of this calculated over 12 months; 3) two hospitalisations within the last 12 months in patients taking and adherent to high dose inhaled steroids (≥1000 µg of beclometasone or equivalent); 4) fixed airflow obstruction with a post bronchodilator FEV_1 <70% of predicted normal.

3.6 *Clinical guidelines*

As described in Section 3.3.1, the main clinical guidelines relevant to the management of severe asthma with elevated eosinophils in the UK are:

- BTS/SIGN British guideline for the management of asthma (22)
- GINA Global Strategy for Asthma Management and Prevention (2016 update) (9)
- International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma (8)

3.7 *Issues relating to current clinical practice*

For patients with severe asthma who remain inadequately controlled with medium to high dose ICS in combination with other controller medications, there are very few treatment options other than continuing to increase the ICS dose or adding OCS (9, 22). However, prolonged use of high-dose inhaled or systemic corticosteroids is associated with several well-known adverse effects, including psychological effects such as irritability, sleep disturbance and increased appetite, severe and potentially life-threatening conditions such as cardiovascular disorders, diabetes and adrenal suppression, and others including decreased bone mineral density, cataracts and glaucoma (23-27). Indeed, the BTS/SIGN guidelines state that ICS should be titrated to the lowest dose at which asthma control is maintained, with dose reductions considered every three months, decreasing the dose by approximately 25–50% each time. OCS should be used at the lowest dose providing adequate control and other treatments should be considered to minimise the use of steroid tablets (22). Similarly, NICE recommends that ICS treatment should be initiated and maintained at the lowest effective dose in order to minimise side effects (65, 66).

Corticosteroid insensitivity is a feature of severe asthma (36-39), with patients experiencing a persistent lack of disease control despite corticosteroid therapy, or worsening of control when corticosteroids are reduced or discontinued. Furthermore, while exacerbations in patients with mild-to-moderate asthma can be effectively treated with high doses of ICS (for example by quadrupling the maintenance dose), this is often not practical in severe asthma as patients are already maintained on high-dose ICS (72, 73). Thus, although corticosteroids are the mainstay of treatment for milder forms of asthma, alternative molecular-targeted therapies are needed in patients with severe asthma (8).

Omalizumab is recommended as an add-on therapy for patients with severe persistent allergic asthma aged six years and older who need continuous or frequent treatment with OCS (24, 28). However, omalizumab does not target the eosinophilic (IL-5-mediated) phenotype and so is unsuitable for patients with severe eosinophilic asthma (see Section 3.3). There is therefore a substantial unmet medical need in patients with severe

asthma and elevated eosinophils inadequately controlled by ICS for effective, targeted treatment options that reduce exacerbations and improve asthma control and symptoms.

3.8 *Equality*

Not applicable. No issues related to equality were identified in the NICE scope.

4 Clinical effectiveness

4.1 *Identification and selection of relevant studies*

A systematic literature review (SLR) was conducted to identify relevant data from the published literature regarding the efficacy and safety of reslizumab versus BSC in adult patients with severe eosinophilic asthma, and versus omalizumab in adult patients with severe persistent allergic (IgE-mediated) asthma. Study selection was based on the PICOS framework (populations, interventions, comparators, outcomes, and study designs); see Appendix 1.

Studies identified through the SLR were used to perform a direct treatment comparison between reslizumab and BSC (see Section 4.9) and an indirect treatment comparison between reslizumab and omalizumab (see Section 4.10). Results from the direct and indirect comparisons were used to inform the cost-effective model in Section 5.

4.1.1 *Search strategy*

The following electronic databases were searched on 02 February 2016: MedLine® (PubMED), Embase®, and the Cochrane library. Additional hand searches were performed between 01 February 2016 and 02 February 2016 for conference abstracts in databases not indexed in Embase® (ERS, ATS, BTS), for clinical trials (Clinicaltrials.gov) and for HTA submissions (NICE, HAS, CADTH, FDA) (Table 10).

Search terms were developed using a combination of MeSH/EMTREE terms and free-text terms to capture different components of the PICOS study question, including population, outcomes and study type. Mepolizumab was included in the search terms in order to capture trials that could be relevant to different countries. However, in the context of the current NICE submission, mepolizumab was excluded as it was not part of the NICE scope. Full details of the search strategy are provided in Appendix 1.

To supplement the systematic searches in electronic databases, hand searches were conducted (12 February 2016) to capture data not reported in the main publications of clinical trials and to capture data from recent, unpublished studies. A list of websites used for the hand searches is provided in Table 10.

Table 10: Hand searches conducted

Source type	Website used for hand searches
Conferences	• 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)
Clinical trials	• Clinicaltrials.gov

Source type	Website used for hand searches
Regulatory documents	• National Institute for Health and Care Excellence (NICE), England • Haute Autorité de Santé (HAS), France • Canadian Agency for Drugs and Technologies in Health (CADTH), Canada • The European Medicines Agency (EMA) • The U.S. Food and Drug Administration (FDA)

4.1.2 *Study selection*

Titles and abstracts (where available) were reviewed by two analysts (one in charge of the primary screening and the second one responsible for the quality check), before full text articles were screened according to the pre-specified eligibility criteria (Table 11). Any discrepancies in the screening were resolved through discussion with a third person. Articles that were identified as potentially relevant during the first phase of the screening were then reviewed in full and assessed for inclusion according to the eligibility criteria.

Null entries or abstracts that were not available were excluded if no further information could be retrieved for that citation. If the information in one publication could be updated by a more recent publication, the former was excluded.

Table 11: Eligibility criteria used in search strategy

	Inclusion criteria	Exclusion criteria
Population	• Severe asthma • Adults	• Non-human • Not severe asthma • Not including adults
Intervention	• Reslizumab (in addition to BSC)	
Comparators	• BSC • Omalizumab (in addition to BSC and in IgE-mediated eosinophilic asthma patients)	
Outcomes	• Asthma control • Exacerbations • Use of oral corticosteroids • Patient and clinician evaluation of response • Lung function • Mortality • Time to discontinuation • Adverse effects of treatment • HRQoL	• Not including at least one outcome of interest based on inclusion criteria[†]
Study design	• RCTs	• Non-randomised studies
Language restrictions	• English	• Any language other than English

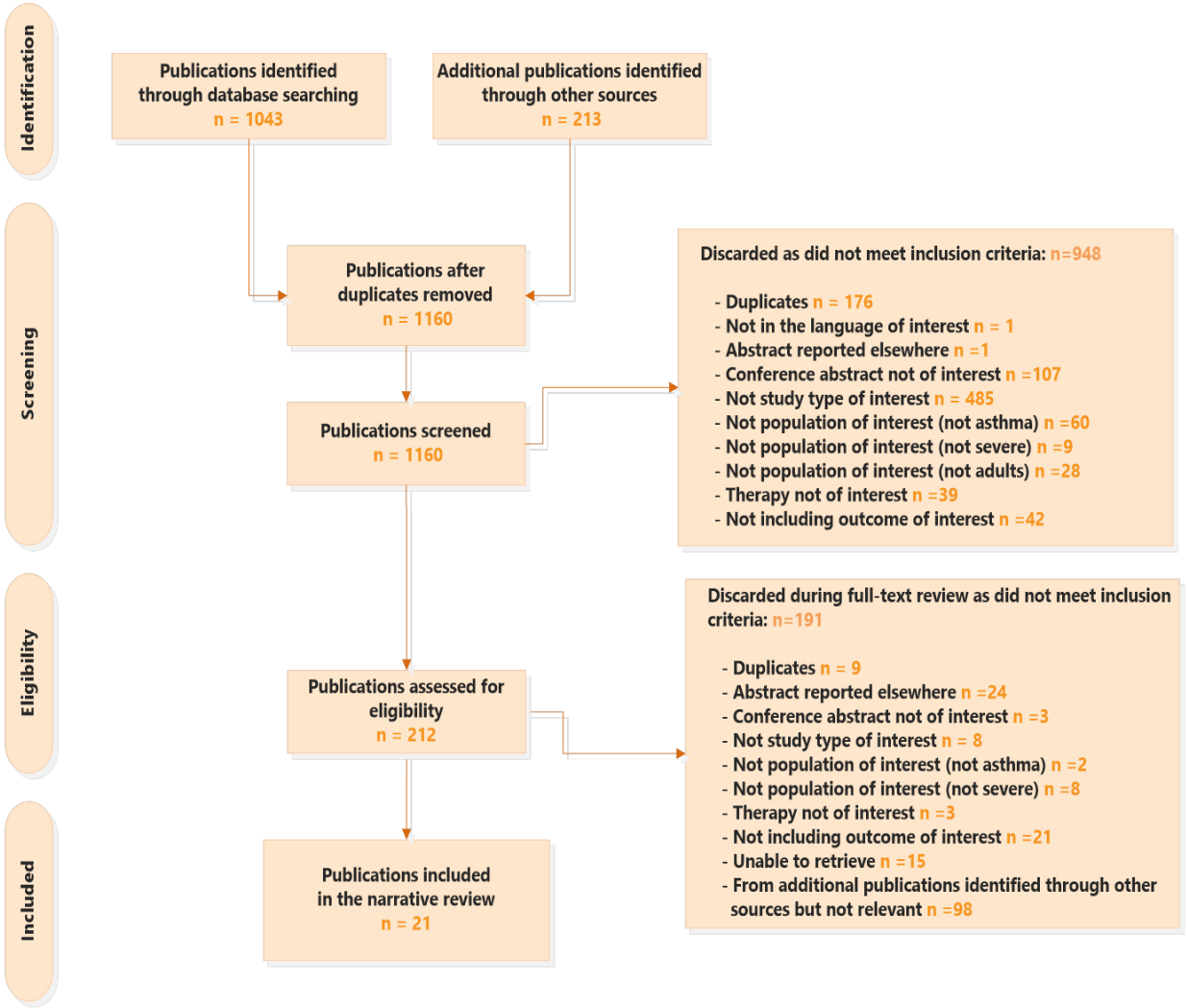
Abbreviations: BSC, best standard of care; HRQoL, health-related quality of life; RCT, randomised controlled trial. [†]i.e. publications not reporting any outcomes related to efficacy or safety were excluded.

A total of 1,256 citations were identified: 1,043 through database searching and 213 through hand searches of other sources. After removal of duplicate papers, 1,160 publications were screened, of which 948 were excluded due to not meeting the inclusion criteria. Two hundred and twelve papers were reviewed in full, of which 191 were excluded with reasons, resulting in the inclusion of 21 studies.

Of the 21 included studies, five were randomised controlled trials (RCTs) evaluating the efficacy and safety of reslizumab and are listed in Table 12 in Section 4.2 (74-78). The remaining 16 RCTs (79-94) provide evidence for one of the comparators of interest to the decision problem (omalizumab; see Table 5 in (95)).

The systematic review schematic is shown in Figure 1. A full list of excluded studies is provided in Appendix 1.

Figure 1: Schematic for the systematic review of clinical evidence



4.2 *List of relevant randomised controlled trials*

The systematic review of clinical evidence identified five RCTs of reslizumab in the population of interest to this submission: C38072/3081, C38072/3082, C38072/3083, C38072/3084 and Res-5-0010 (Table 12). Placebo was the comparator in all five studies.

The publication by Castro et al (96) for C38072/3082 and C38072/3083 was identified through the SLR but was recorded as a duplicate and excluded during the screening process because the sponsor's CSRs report these trials in more detail. Since the SLR was conducted in February 2016, manuscripts for C38072/3081 and C38072/3084 have also been accepted for publication (97, 98) and are therefore cited in Table 12.

Table 12: List of relevant RCTs

Trial no. (acronym)	Population	Intervention	Comparator	Primary study ref(s)	Refs identified but not used further	Is study excluded from further discussion? If yes state rationale
Phase III studies						
C38072/3082 ('Study 3082')	Patients aged 12–75 years with asthma and elevated blood eosinophils (≥400/μL) inadequately controlled with medium to high dose ICS	Reslizumab 3.0 mg/kg	Placebo	Castro et al, 2015 (96) and the clinical study report (76)	–	No (pivotal study)
C38072/3083 ('Study 3083')	Patients aged 12–75 years with asthma and elevated blood eosinophils (≥400/μL) inadequately controlled with medium to high dose ICS	Reslizumab 3.0 mg/kg	Placebo	Castro et al, 2015 (96) and the clinical study report (77)	–	No (pivotal study)
C38072/3081 ('Study 3081')	Patients aged 12–75 years with asthma and elevated blood eosinophils (≥400/μL) inadequately controlled with medium to high dose ICS	Reslizumab 0.3 mg/kg; reslizumab 3.0 mg/kg	Placebo	Bjermer et al, 2016 (97) and the clinical study report (75)	–	No (pivotal study)
C38072/3084 ('Study 3084')	Adult patients with moderate to severe asthma uncontrolled with medium to high dose ICS	Reslizumab 3.0 mg/kg	Placebo	Corren et al, 2016 (98) and the clinical study report (78)	–	No (supporting study due to different eligibility criteria to the pivotal Phase III studies)
Phase II studies						
Res-5-0010	Adult patients with asthma and eosinophilic airway inflammation (sputum eosinophils ≥3%)	Reslizumab 3.0 mg/kg	Placebo	Castro et al, 2011 (74)	–	Yes. Phase II proof of concept study that informed the Phase III clinical programme

Abbreviations: ICS, inhaled corticosteroids; NA, not applicable; RCT, randomised controlled trial.

4.3 *Summary of methodology of the relevant randomised controlled trials*

4.3.1 *Comparative summary of RCT methodology*

The methodology of the pivotal Phase III RCTs is summarised in Table 13.

Table 13: Comparative summary of methodology of the RCTs

Trial no. (acronym)	Study 3082	Study 3083	Study 3081
Study objective	**Primary objective** To demonstrate the efficacy of reslizumab at a dose of 3.0 mg/kg administered intravenously every 4 weeks over 52 weeks, as assessed by the reduction in frequency of CAEs during the 52-week treatment period. **Secondary objectives** To assess the following: • Change from baseline in FEV_1, AQLQ score, ACQ score, ASUI score, SABA use, and blood eosinophil count • Time to first CAE		**Primary objective** To determine whether reslizumab, at a dose of 0.3 mg/kg or 3.0 mg/kg administered every 4 weeks for a total of 4 doses, was more effective than placebo in improving lung function as assessed by the overall change from baseline in FEV_1. **Secondary objectives** To assess the following: • Efficacy as assessed by ACQ, AQLQ, lung function (FEV_1,% predicted FEV_1, FVC and $FEF_{25–75\%}$), ASUI, SABA use and blood eosinophil count • Pharmacokinetics • Relationship between reslizumab serum concentration and measures of efficacy and safety • Safety and tolerability • Immunogenicity
Design	Phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group, fixed-dosage study in patients with asthma and elevated blood eosinophils (≥400/µL) inadequately controlled by medium to high dose ICS.		Phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group, fixed dosage study in patients with asthma and elevated blood eosinophils (≥400/µL).
Duration of study	April 2011 to March 2014.	March 2011 to April 2014	February 2011 to September 2013

Trial no. (acronym)	Study 3082	Study 3083	Study 3081
	• Screening period: 2–4 weeks • Treatment period: 52 weeks including a final evaluation at Week 52 (end-of-treatment visit 4 weeks after the final infusion at Week 48) • At study-end, patients were enrolled in an open-label extension study (C38072/3085) or returned for a follow-up assessment 90 (±7) days after the end-of-treatment visit		• Screening period: 2–4 weeks • Treatment period: 16 weeks including a final evaluation (end-of-treatment visit) 4 weeks after the final infusion • At study-end, patients were enrolled in an open-label extension study (C38072/3085) or returned for a follow-up assessment 90 (±7) days after the end-of-treatment visit
Method of randomisation	Patients were randomised using a qualified randomisation service provider using IRT (computerised central randomisation) in a 1:1 ratio to receive either reslizumab or placebo. Randomisation was stratified by: • Maintenance oral corticosteroid use at study enrolment (yes/no) • Region (US/other)		Patients were randomised using IRT in a 1:1:1 ratio to receive reslizumab (0.3 mg/kg or 3.0 mg/kg) or placebo. Randomisation was stratified by: • Previous asthma exacerbations within the past 12 months (yes/no) • Age at baseline (12–17 years or ≥18 years)
Method of blinding (care provider, patient and outcome assessor)	Patients and investigators remained blinded to treatment assignment during the study. The sponsor's clinical personnel were also blinded to study drug identity until the database was locked for analysis and the treatment assignment revealed.		
Key eligibility criteria	Eligible patients were aged 12–75 years with asthma and a blood eosinophil count ≥400/µL. Details of inclusion and exclusion criteria are provided in Section 4.3.2.		
Settings and locations where the data were collected	Patients were randomised at 102 sites in 17 countries (Australia, Belgium, Chile, Columbia, Czech Republic, Denmark, Hungary, Israel, Malaysia, New Zealand, Philippines, Poland, Russia, South Africa, Sweden, Thailand and USA).	Patients were randomised at 82 centres in 15 countries (Argentina, Brazil, Canada, France, Germany, Greece, Republic of Korea, Mexico, Peru, Romania, Russia, Slovak Republic, Taiwan, Ukraine and USA).	Patients were randomised at 68 centres in 12 countries (Argentina, Belgium, Brazil, Canada, Colombia, Hungary, Israel, Mexico, Netherlands, Poland, Sweden and USA).
Trial drugs (the	• Reslizumab 3.0 mg/kg (N=245)	• Reslizumab 3.0 mg/kg (N=232)	• Reslizumab 0.3 mg/kg (N=104)

Trial no. (acronym)	Study 3082	Study 3083	Study 3081
interventions for each group with sufficient details to allow replication, including how and when they were administered)	• Placebo (N=244)	• Placebo (N=232)	• Reslizumab 3.0 mg/kg (N=106) • Placebo (N=105)
	Study drugs were administered by intravenous infusion over 15–30 minutes once every 4 weeks (±7 days) for a total of 13 doses. The dose was adjusted if there was a change from baseline in body weight of ≥10%.		Study drugs were administered by intravenous infusion once every 4 weeks for 12 weeks. Baseline body weight was used to determine dose throughout the study.
Intervention(s) (n=[x]) and comparator(s) (n=[x])	Study drugs were provided in 10 mL vials. • Reslizumab was formulated at 10 mg/mL in 20 mM sodium acetate, 7% sucrose, pH 5.5 buffer • Placebo was formulated in 20 mM sodium acetate, 7% sucrose, pH 5.5 buffer		
Permitted and disallowed concomitant medications	Baseline asthma therapy regimen was to be unchanged throughout the study (including, but not limited to, LABAs, inhaled corticosteroids, oral corticosteroids [≤10 mg prednisone daily or equivalent], leukotriene antagonists, 5-lipoxygenase inhibitors, and cromolyn sodium). Prohibited medications were: • Anti-hIL-5 monoclonal antibody, including reslizumab, mepolizumab and benralizumab Medications restricted prior to baseline (with corresponding washout times) were: • Systemic corticosteroids (30 days); oral corticosteroids ≤10 mg prednisone daily or equivalent were allowed if the dosage was stable for 30 days prior to screening and continued without dosage changes throughout the study) • Any immunosuppressive or immunomodulatory agents, including, but not limited to, methotrexate, cyclosporin, and interferon-α (6 months) • Anti-TNF monoclonal antibody (6 months) • All other non-biologic investigational drugs (30 days) • Live attenuated vaccines (12 weeks) • All other biologic therapies, including omalizumab (Xolair®; 6 months) Patients were to refrain from using SABAs for 6 hours, and LABAs for		Baseline asthma therapy regimen was to be unchanged throughout the study (including but not limited to inhaled corticosteroids, leukotriene antagonists, 5-lipoxygenase inhibitors and cromolyn). Prohibited medications were: • Anti-hIL-5 monoclonal antibody, including reslizumab, mepolizumab and benralizumab Medications restricted prior to baseline (with corresponding washout times) were: • Systemic (including oral) corticosteroids (30 days) • Any immunosuppressive or immunomodulatory agents, including, but not limited to, methotrexate, IgE monoclonal antibody, cyclosporin, and interferon-α (6 months) • Anti-TNF monoclonal antibody (6 months) • All other non-biologic investigational drugs (30 days) • Live attenuated vaccines (12 weeks) • Investigational biologic therapies (90 days from

Trial no. (acronym)	Study 3082	Study 3083	Study 3081
	12 hours, prior to any study visit that included spirometry or airway reversibility testing, including the screening visit.		screening) • All other biologic therapies, including omalizumab (Xolair®; 6 months). Patients were to refrain from using SABAs for 6 hours, and LABAs for 12 hours, prior to any study visit, including screening.
Primary outcome (including scoring methods and timings of assessments)	**Primary analysis of the primary efficacy outcome** Frequency of CAEs during the 52-week treatment period (see further details in Section 4.3.3) **Secondary analyses of the primary efficacy outcome** • Frequency of CAEs requiring oral or systemic corticosteroids for ≥3 days • Frequency of asthma exacerbations resulting in hospitalisation or a visit to the emergency room		**Primary analysis of the primary efficacy outcome** • Change from baseline in FEV_1 over 16 weeks **Secondary analyses of the primary efficacy outcome** • Change from baseline in FEV_1 over 16 weeks for the FEV_1 analysis set (the subpopulation of patients in the FAS with % predicted FEV_1 ≤85% at baseline; see Section 4.4.1)
Secondary/tertiary outcomes (including scoring methods and timings of assessments)	**Secondary efficacy outcomes** • Change from baseline in FEV_1 to Week 16 • Overall change from baseline in FEV_1 over 16 weeks • Change from baseline in AQLQ score to Week 16 • Overall change from baseline in ACQ score over 16 weeks • Time to first CAE • Overall change from baseline in ASUI score over 16 weeks • Overall change from baseline in SABA use over 16 weeks • Overall change from baseline in blood eosinophil count over 16 weeks and 52 weeks		**Secondary efficacy outcomes** • Change from baseline to Weeks 4, 8, 12, and 16 or early withdrawal in: lung function (FEV_1, FVC, $FEF_{25–75\%}$ and % predicted FEV_1); ACQ score; ASUI score; and SABA use • Change from baseline to Week 16 or early withdrawal in AQLQ score • Change from baseline to Weeks 4, 8, 12 and 16, and follow-up or early withdrawal in blood eosinophil count

Trial no. (acronym)	Study 3082	Study 3083	Study 3081
Other/exploratory efficacy outcomes	**Other efficacy outcomes** • Change from baseline to Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 or early withdrawal, in: lung function (FEV_1 [except Week 16], % predicted FEV_1, FVC, and $FEF_{25–75\%}$); ASUI score; ACQ score; and SABA use • Change from baseline to Weeks 16, 32, and 52 or early withdrawal, in AQLQ score • Change from baseline to Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52, and follow-up or early withdrawal, in blood eosinophil count		**Other efficacy outcomes** None reported
	Exploratory variables • Sputum eosinophils and biomarkers: Selected study centres only; samples were collected at baseline and Week 52, or early withdrawal • Change from baseline in PEFR: Measurements were collected to support the primary analysis of CAE frequency, and as an exploratory measure of ambulatory lung function. PEFR was recorded at baseline and each morning and evening before administration of regular asthma medication • Fibulin-1 (blood biomarker of lung tissue remodelling), collected at baseline and Weeks 12, 24, 36 and 48 • Nasal polyps: Optional assessment at participating US	**Exploratory variables** • Sputum eosinophils and biomarkers: Selected study centres only; samples were collected at baseline and Week 52 • Change from baseline in PEFR: Measurements were collected to support the primary analysis of CAE frequency, and as an exploratory measure of ambulatory lung function. PEFR was recorded at baseline and each morning and evening before administration of regular asthma medication	**Exploratory variables** • Sputum eosinophils: Selected study centres only; measured at baseline and endpoint • Biomarkers: Blood samples were collected at screening, baseline, and at Weeks 8 and 16 or early withdrawal to evaluate changes in ECP and EDN (indicators of eosinophilic inflammation) and EP (a marker of airway eosinophilia) • Nasal polyps: Subset of patients aged ≥18 years at participating US centres; the number, size and location of nasal polyps were assessed by CT

Trial no. (acronym)	Study 3082	Study 3083	Study 3081
	study centres; the number, size and location of nasal polyps were assessed by CT at baseline and Week 52 • IgE: Blood samples were collected at baseline and at Week 52 or early withdrawal		
Pre-planned subgroups	The following subgroup analyses were pre-specified: • CAE frequency by the type of medical intervention required to treat the event • Change from baseline in FEV_1 in the subpopulation of patients in the FAS with % predicted FEV_1 ≤85% at baseline (the FEV_1 analysis set) • Time to first CAE in the subpopulation of patients who had CAEs requiring treatment with systemic corticosteroids		The following subgroup analysis was pre-specified: • Change from baseline in FEV_1 in the subpopulation of patients in the FAS with % predicted FEV_1 ≤85% at baseline (the FEV_1 analysis set)

Abbreviations: ACQ, Asthma Control Questionnaire; ASUI, Asthma Symptom Utility Index; AQLQ, Asthma Quality of Life Questionnaire; CAE, clinical asthma exacerbation; CBC, complete blood count; CT, computerised tomography; ECP, eosinophil cationic protein; EDN, eosinophil-derived neurotoxin; EP, eosinophilic peroxidase; FEV_1, forced expiratory volume in one second; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IRT, Interactive Response Technology; LABA, long-acting beta-agonist; PEFR, peak expiratory flow rate; SABA, short-acting beta-agonist.

4.3.2 *Eligibility criteria*

Key eligibility criteria for the pivotal Phase III RCTs are summarised in Table 14.

Table 14: Eligibility criteria for RCTs

Trial no. (acronym)	C38072/3082	C38072/3083	C38072/3081
Inclusion criteria	• Adults aged 12–75 years† with a previous diagnosis of asthma • Blood eosinophil count ≥400 cells/μL • ≥1 asthma exacerbation requiring corticosteroid use for at least 3 days in the 12 months prior to screening (**3082 and 3083 only**; no eligibility criterion relating to asthma exacerbations was stated in the CSR for 3081) • Airway reversibility of ≥12% after beta-agonist administration • ACQ score ≥1.5 • Current treatment with inhaled fluticasone ≥440 μg, or equivalent, daily. Stable baseline asthma therapy regimen for 30 days prior to screening. • Female patients were to be surgically sterile, 2 years postmenopausal or have a negative pregnancy test at screening and baseline. Females of childbearing potential were to use a medically accepted method of contraception throughout the study and for 30 days after participation in the study. • In reasonable health (except for asthma diagnosis) as judged by the investigator and as determined by medical history, medical examination, ECG evaluation, serum chemistry, haematology, serology (C38072/3081 only) and urinalysis • Willing and able to comply with the study		
Exclusion criteria	• Clinically meaningful comorbidity that would interfere with the study or compromise patient safety • Hypereosinophilic syndrome • Confounding underlying lung disorder (e.g. chronic obstructive pulmonary disease, pulmonary fibrosis or lung cancer) • Pulmonary condition with symptoms of asthma and blood eosinophilia (e.g. Churg-Strauss syndrome or allergic bronchopulmonary aspergillosis) • Has smoked within 6 months prior to screening • Previous treatment with an anti-hIL-5 monoclonal antibody • Any aggravating, inadequately-controlled medical factor (e.g. rhinitis, gastroesophageal reflux disease or diabetes) • Participation in any investigative drug or device study within 30 days prior to screening • Concurrent infection or disease that could preclude assessment of active asthma		

	• History of concurrent immunodeficiency (HIV, AIDs or congenital immunodeficiency)‡ • Receipt of any live attenuated vaccine within 12 weeks prior to screening • History of allergic reactions to or hypersensitivity to any component of the study drug • Female patients who were pregnant, nursing, or of childbearing potential and not using a medically-accepted, effective method of birth control • Suspected current drug or alcohol abuse	
	• Use of systemic immunosuppressive, immunomodulating, or other biologic agents within 6 months prior to screening • Participation in any investigative biologics study within 6 months prior to screening • Active parasitic infection within 6 months prior to screening • Infection requiring hospital admission for ≥24 hours, intravenous antibiotics or oral antibiotics within 4 weeks prior to screening or during the screening period • History of exposure to water-borne parasites within 6 weeks prior to screening or during the screening period or a history of diarrheal illness of undetermined aetiology within 3 months prior to screening or during the screening period • Treatment for an asthma exacerbation required within 4 weeks of screening or during the screening period	• Current use of systemic (including oral) corticosteroids • Use of systemic immunosuppressive or immunomodulating agents within 6 months prior to screening • Participation in any investigative biologics study within 90 days prior to screening • Presence of or suspected parasitic infestation/infection • Expected to be poorly compliant with study drug administration, study procedures or visits

Abbreviations: ACQ, Asthma Control Questionnaire; AIDS, acquired immune deficiency syndrome; CSR, clinical study report; ECG, electrocardiography; HIV, human immunodeficiency virus; RCT, randomised controlled trial.
†In C38072/3083, patients aged 12–17 years were excluded from participating in Germany, India, Argentina, and Korea; patients aged 66–75 years were excluded from participating in India and Korea. In C38072/3081, patients aged 12–17 years were excluded from participating in Argentina. ‡In C38072/3083 and C38072/3081, patients in Argentina must have had documented serology testing for HIV performed during screening.

4.3.3 *Definitions and appropriateness of outcome measures*

Table 15: Efficacy measures used in Studies 3082, 3083 and 3081

Outcome(s) and measures	Included in NICE scope?	Reliability/validity/current use in clinical practice
Frequency of CAEs (3082 and 3083 only)[†] An exacerbation event was defined as a CAE if the patient met either or both of the following criteria: • 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. • 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 FEV_1 by ≥20% from baseline • Decrease in PEFR by ≥30% from baseline on two consecutive days • 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 eCRF; asthma worsenings recorded in the eCRF are referred to as investigator-determined CAEs.	Yes	As described in Section 3.2.1, asthma exacerbations lead to morbidity, can be life threatening, and are thought to be the primary cause of asthma-related hospital admissions. In the reslizumab trials an adjudication committee was formed to ensure uniformity in determining whether an investigator-determined CAE fulfilled the required criteria. The committee remained blinded to treatment allocation. Adjudicated outcomes were considered final for the purpose of analysis and reporting.
Lung function Values measured by spirometry in the reslizumab clinical trials were: • **FEV_1:** The volume of air expelled in the first second of a forced expiration. • **FVC:** The volume of air that can be forcibly blown out after full inspiration.	Yes	Lung function, particularly FEV_1, is an important indicator of future risk of adverse asthma outcomes. It should be recorded at diagnosis, 3–6 months after starting treatment to measure the patient's personal best lung function, and

• **$FEF_{25–75\%}$:** The forced expiratory flow at 25–75% of the FVC. • **% predicted FEV_1:** The ratio of the volume of air expired in the first second of a forced expiration to the patient's predicted FEV. • **PEFR:** The greatest rate of airflow that can be obtained during a forced exhalation.		periodically thereafter for ongoing risk assessment (9). Lung function testing is most commonly performed using spirometry, which measures the volume of air that can be breathed out in one forced breath (99).
AQLQ score Quality of life was measured using the AQLQ (100), which comprises 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 and responses were assessed using a 7-point scale, with 7 indicating no impairment and 1 indicating severe impairment.	Yes (HRQoL included in scope)	The AQLQ is a well-validated quality of life questionnaire, and is recommended in the BTS/SIGN guidelines (22).
ACQ score Asthma control was measured using the ACQ, which is comprised of 7 questions, each with a possible score ranging from 0–6 (a higher score indicates poorer asthma control). The total score is the mean of all responses. Six of the questions are self-assessments; one is the result of the patient's % predicted FEV_1 measurement.	Yes (asthma control included in scope)	The ACQ is validated, widely-used (101), and is one of the tools recommended in both the BTS/SIGN and GINA guidelines for the assessment of symptomatic asthma control (9, 22). Asthma symptom control should be assessed at every opportunity as asthma symptoms contribute to the burden of disease for the patient and are associated with an increased risk of exacerbations (9).
ASUI score An asthma symptom score was produced using the ASUI assessment too, an 11-item instrument to assess the frequency and severity of asthma symptoms and side effects, weighted by patient preferences.	Yes (asthma control included in scope)	ASUI is a reliable and validated assessment tool that is responsive to changes in asthma control over time (102, 103).
SABA use Patients were asked to recall whether SABAs were used within 3 days of the scheduled visit and, if so, how many puffs were used.	No	High SABA use is a risk factor for asthma exacerbations. Excessive use (i.e. more than 200 doses per month) is a risk factor for increased mortality (9).
Blood eosinophil count Blood eosinophil count was measured using a standard CBC with differential blood test.	No	As described in Section 3.1.2, measurement of eosinophils in blood is a practical biomarker of eosinophilic

		inflammation in asthma, and has been shown to closely correlate with sputum eosinophil levels (14, 42-44).

Abbreviations: ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; ASUI, Asthma Symptom Utility Index score; CAE, clinical asthma exacerbation; CBC, complete blood count; eCRF, electronic case report form; FEF, forced expiratory flow; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; HRQoL, health-related quality of life; PEFR, peak expiratory flow rate; SABA, short-acting beta agonist.

[†]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 AE 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.

4.4 *Statistical analysis and definition of study groups in the relevant randomised controlled trials*

4.4.1 *Populations analysed*

4.4.1.1 Randomised set

The randomised set (RS) was defined as all randomised patients, regardless of whether or not a patient received any study drug.

- In C38072/3082 and C38072/3083 the RS was used for all study population summaries and efficacy analyses unless otherwise stated.
- In C38072/3081 the RS was used for all study population summaries unless otherwise noted.

4.4.1.2 Full analysis set

The full analysis set (FAS) was defined as all randomised patients who were treated with at least one dose of study drug.

- In C38072/3082 and C38072/3083 the FAS was used for confirmatory analyses.
- In C38072/3081 the FAS was used for all efficacy analyses unless otherwise stated.

Data on pulmonary function, SABA use, and Asthma Control Questionnaire (ACQ), Asthma Quality of Life Questionnaire (AQLQ) and Asthma Symptom Utility Index (ASUI) at a scheduled visit were excluded from the FAS if medications that could significantly confound interpretation of the efficacy parameters were used within 7 days prior to the assessment. The included medications for each trial are listed below.

- C38072/3082 and C38072/3083: Addition of a LABA, a long-acting muscarinic-antagonist (LAMA), or an oral or systemic corticosteroid, if not taken at baseline. If taken at baseline, an increase in a chronic, maintenance dose of oral/systemic corticosteroid was included.
- C38072/3081: 1) oral or systemic corticosteroids, or 2) addition of a LABA or LAMA if not taken at baseline.

4.4.1.3 Safety analysis set

The safety analysis set (SAS) was defined as all patients who received at least one dose of study drug. The SAS was used for all safety analyses unless otherwise noted.

4.4.1.4 FEV_1 analysis set

The subpopulation of patients in the FAS with % predicted FEV_1 ≤85% at baseline.

4.4.2 *Statistical information*

A summary of the statistical methods used in the pivotal Phase III reslizumab trials is presented in Table 16.

Table 16: Summary of statistical analyses in RCTs

Trial no. (acronym)	C38072/3082	C38072/3083	C38072/3081
Hypothesis	The clinical objective of C38072/3082 and C38072/3083 was to demonstrate the efficacy of reslizumab, at a dose of 3.0 mg/kg administered intravenously every 4 weeks over 52 weeks.		The clinical objective of C38072/3081 was to determine whether reslizumab, at a dose of 0.3 mg/kg or 3.0 mg/kg administered once every 4 weeks for a total of 4 doses, was more effective than placebo in improving lung function.
Multiple comparisons and multiplicity	A pre-specified, fixed-sequence multiple testing procedure was applied to the primary efficacy variable and the eight secondary efficacy variables listed in Table 13 to control the Type 1 error rate for multiple testing. If the two-sided p-value from the primary variable comparison was ≤0.05, the next comparison of interest (first secondary variable) was interpreted inferentially at 0.05. This process continued through the secondary variables in the order specified (Table 13) until all comparisons of interest were interpreted inferentially, or until the two-sided p-value for a comparison was >0.05, at which point no further comparisons were interpreted inferentially. Results of testing the frequency of CAEs specifically requiring systemic corticosteroids could be interpreted inferentially at an alpha level of 0.05 provided that results of all tests for secondary variables were significant. Analyses of other and exploratory efficacy variables were not adjusted for multiple testing and thus p-values are nominal.		A pre-specified, hierarchical testing procedure was applied to the primary efficacy variable to control the Type I error rate for the two comparisons of reslizumab vs placebo. Statistical significance was claimed in the order of reslizumab 3.0 mg/kg first and 0.3 mg/kg second. Specifically, a treatment effect was considered significant for reslizumab 3.0 mg/kg if the p-value was ≤0.05. Significance was claimed for both reslizumab doses if the p-values were both ≤0.05. No significance was claimed otherwise. The secondary analysis of the primary efficacy variable, and analyses of secondary efficacy variables, were not adjusted for multiple testing and thus p-values are nominal.
Analysis of primary endpoint	**Primary analysis of the primary efficacy outcome** The frequency of CAEs was analysed using the 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. Treatment effect was tested using the likelihood-based Chi-square test at the 0.05 significance level.		**Primary analysis of the primary efficacy outcome** Change from baseline in FEV_1 over 16 weeks was analysed using a 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. An unstructured covariance matrix was used for within-patient correlation modelling. In case there was a convergence problem with the unstructured covariance, a first order autoregressive covariance structure (AR1) was

Trial no. (acronym)	C38072/3082	C38072/3083	C38072/3081
			assumed. Treatment difference (and 95% CI) was estimated from the MMRM. Treatment effect was tested using a 2-sided t-test at the 0.05 significance level.
	Sensitivity analyses of the primary efficacy outcome To assess the robustness of the primary analysis, two sensitivity analyses were performed: 1. Analysis using an offset variable that did not exclude the summed duration of CAEs from the follow-up time 2. Analysis using a multiple imputation method for missing data (104) to evaluate whether the primary analysis model was unbiased in terms of patterns of missing data (CAE and exposure data for patients who withdrew early were imputed).		**Sensitivity analyses of the primary efficacy outcome** To assess the robustness of the primary analysis, two sensitivity analyses were performed: 1. Analysis using all FEV_1 measurements without data exclusions for confounding medications (see Section 4.4.1.2) 2. Analysis using a multiple imputation method for missing data (104) and excluding data for which concomitant medications could confound interpretation (i.e. using the FAS).
	Secondary analyses of the primary efficacy outcome Secondary analyses were performed similarly to the primary efficacy endpoint based on the randomised set.		**Secondary analyses of the primary efficacy outcome** The secondary analysis was performed similarly to the primary efficacy endpoint.
Analysis of secondary and other efficacy endpoints	• Pulmonary function tests, blood eosinophil counts, SABA use, and ACQ, AQLQ and ASUI scores were analysed using a MMRM with treatment, visit, treatment and visit interaction, and stratification factors as fixed effects and patients as a random effect. Covariates were included in the model (for pulmonary function tests, covariates for height and sex were also included). • Time to CAE was analysed using the Kaplan-Meier method. The hazard ratio and p-value were estimated using the stratified Cox regression model. • Change from baseline in pulmonary function tests was analysed using an ANCOVA model with fixed effects for treatment, stratification factors and sex, and covariates for height and baseline value. • Change from baseline in AQLQ score was analysed using the same		• Pulmonary function tests, blood eosinophil counts, SABA use, and ACQ, AQLQ and ASUI scores were analysed using the same MMRM model as for the primary efficacy variable • The Cochran Mantel Haenszel test (stratified by age group and asthma exacerbation category) was used to analyse the proportions of patients achieving a ≥0.5 reduction in ACQ score, and the proportion of patients achieving a ≥0.5 improvement in AQLQ score, from baseline to each scheduled visit.

Trial no. (acronym)	C38072/3082	C38072/3083	C38072/3081
	ANCOVA model with the exception of inclusion of sex and height in the model. • Proportions of patients achieving a ≥0.5 reduction in ACQ score and a ≥0.5 improvement in AQLQ score were analysed using the stratified Cochran-Mantel-Haenszel test.		
Analysis of exploratory variables	• Change from baseline in weekly average PEFR was analysed using a MMRM with treatment, visit, treatment and visit interaction, stratification factors and sex as fixed effects, patient as a random effect, and covariates for height and baseline value. • Data on sputum eosinophils, biomarkers and IgE were summarised using descriptive statistics.	• Change from baseline in weekly average PEFR was analysed using a MMRM with treatment, visit, treatment and visit interaction, stratification factors and sex as fixed effects, patient as a random effect, and covariates for height and baseline value. • Data on sputum eosinophils were summarised using descriptive statistics.	• Data on sputum eosinophils, biomarkers and nasal polyps were summarised using descriptive statistics.
Sample size and power calculation	480 patients (240 per group) provided approximately 90% power at the 0.05 significance level to detect a 33% reduction in CAE rate with reslizumab versus placebo, assuming a CAE rate of 1.2 per year for the placebo group. This estimate accounted for a maximum 10% false positive rate for the blood eosinophil test at enrolment and a 9% dropout rate in both treatment groups.	460 patients (230 per group) provided approximately 90% power at the 0.05 significance level to detect a 33% reduction in CAE rate with reslizumab versus placebo, assuming a CAE rate of 1.2 per year for the placebo group. This estimate accounted for a maximum 10% false positive rate for the blood eosinophil test at enrolment and a 5% dropout rate in both treatment groups.	300 patients (100 per group) provided at least 90% power at the 0.05 significance level to detect a difference in change from baseline in FEV_1 between a reslizumab dose (3.0 mg/kg or 0.3 mg/kg) and placebo, using a 2-sided t-test and by MMRM simulation. This estimate assumed an equal effect size for both reslizumab doses.
Data	For efficacy analyses, assessments collected at the early withdrawal visit		Missing data were not imputed in the primary MMRM

Trial no. (acronym)	C38072/3082	C38072/3083	C38072/3081
management, patient withdrawals	were considered as the next scheduled visit if they were performed at least 3, but no more than 5 weeks since the last study drug administration. All available data were included for evaluation. Missing or invalid values were not imputed unless otherwise specified. A low (<5%) dropout rate was anticipated because all patients maintained their background therapies throughout the study; all efforts were made to treat and retain patients after CAEs. The primary analysis model was unbiased if the missing data mechanism appeared to be random. As described above, a sensitivity analysis using imputation for missing data was performed to assess the robustness of the primary model. Missing or invalid laboratory test results were not estimated for biomarker analysis and safety analysis.		analysis. The primary analysis was unbiased if the missing data mechanism was ignorable. As described above, a sensitivity analysis using imputation for missing data was performed to assess the robustness of the primary analysis.

Abbreviations: ACQ, Asthma Control Questionnaire; ANCOVA, analysis of covariance; AQLQ, Asthma Quality of Life Questionnaire; ASUI, Asthma Symptom Utility Index; CAE, clinical asthma exacerbation; CI, confidence interval; CT, computerised tomography; FAS, full analysis set; FEV_1, forced expiratory volume in one second; IgE, immunoglobulin E; MMRM, mixed-effect model for repeated measures; PEFR, peak expiratory flow rate; RCT, randomised controlled trial; SABA, short-acting beta-agonist.

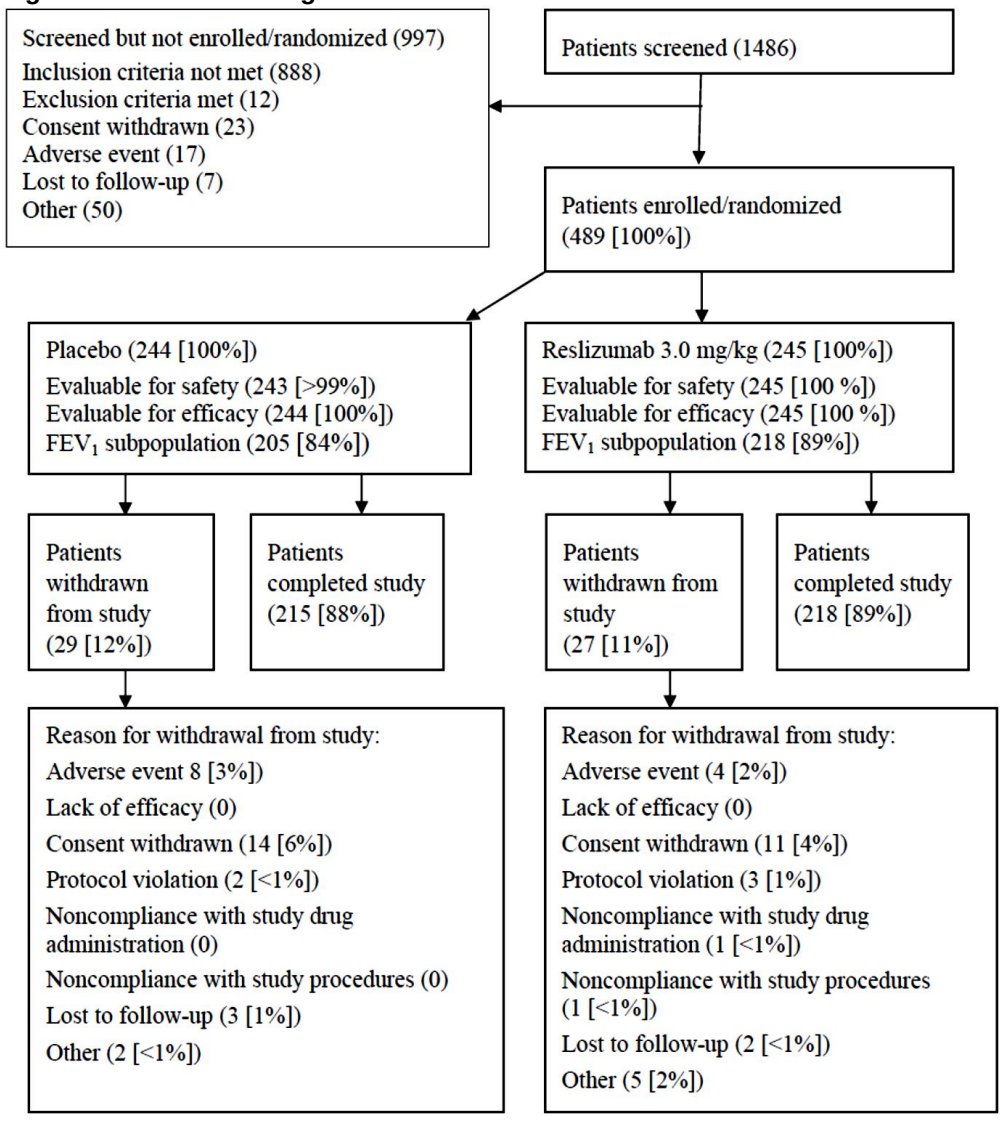
4.5 *Participant flow in the relevant randomised controlled trials*

4.5.1 *Patient disposition*

4.5.1.1 C38072/3082

A total of 489 patients (randomised set) were randomly assigned to treatment (245 in the reslizumab group and 244 in the placebo group). One (<1%) patient randomised to receive placebo was withdrawn due to a protocol violation before receiving any study drug; 488 (>99%) patients received at least one dose of study drug and were included in the FAS. Of the 489 randomised patients, 433 (89%) completed the study. The most common reasons for study discontinuation in both treatment groups were 'consent withdrawn' (11 [4%] and 14 [6%] patients, respectively) and 'AEs' (4 [2%] and 8 [3%] patients, respectively). A CONSORT diagram for C38072/3082 is presented in Figure 2.

Figure 2: CONSORT diagram for C38072/3082

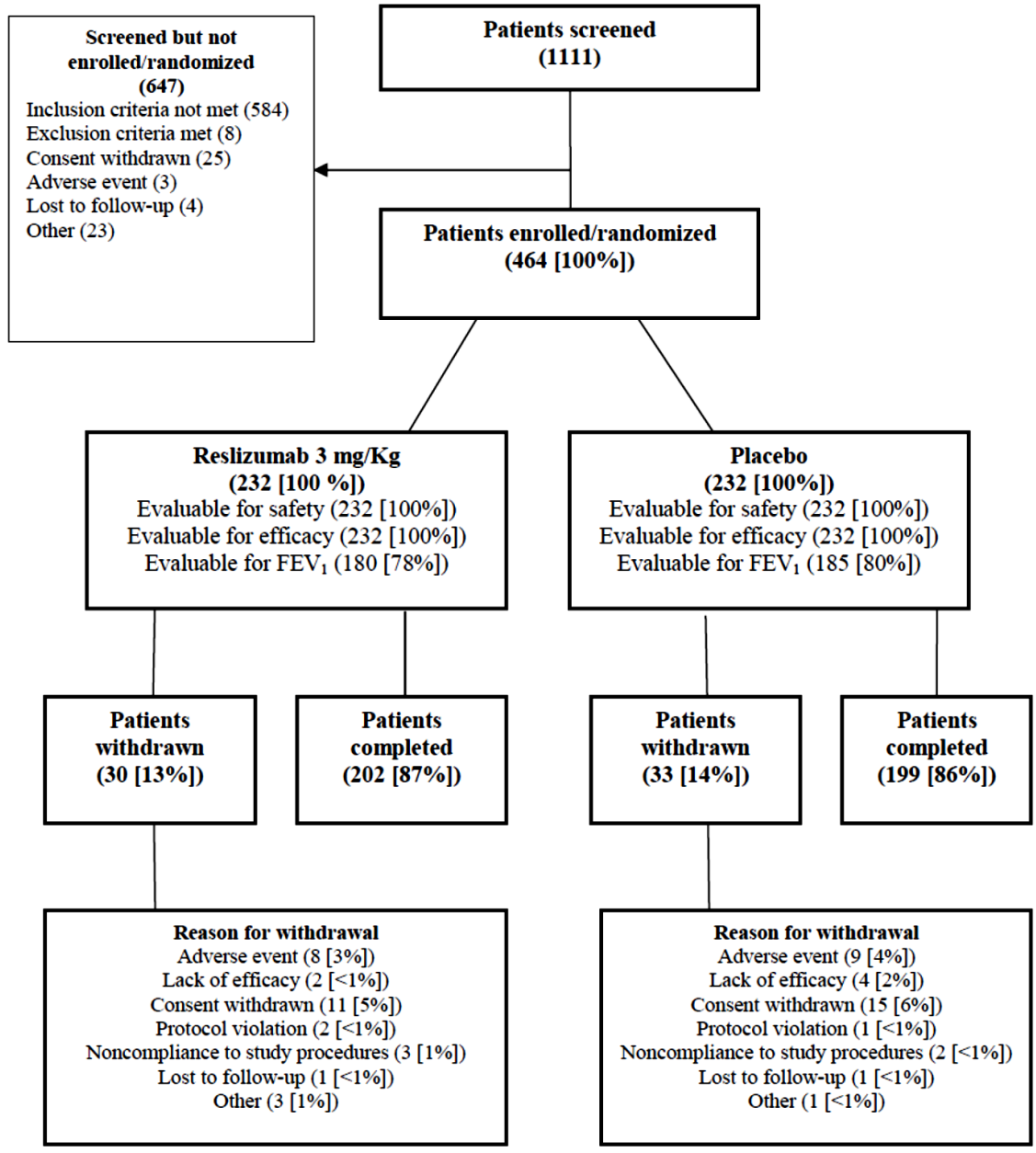


Abbreviations: FEV_1, forced expiratory volume in one second.

4.5.1.2 C38072/3083

A total of 464 patients (randomised set) were randomly assigned to treatment (232 in the reslizumab group and 232 in the placebo group). All randomised patients received at least one dose of study drug and were included in the FAS. Of the 464 randomised patients, 401 (86%) completed the study. The most common reasons for study discontinuation in both the reslizumab and placebo groups were 'consent withdrawn' (11 [5%] and 15 [6%] patients, respectively) and 'AEs' (8 [3%] and 9 [4%] patients, respectively). A CONSORT diagram for C38072/3083 is presented in Figure 3.

Figure 3: CONSORT diagram for C38072/3083



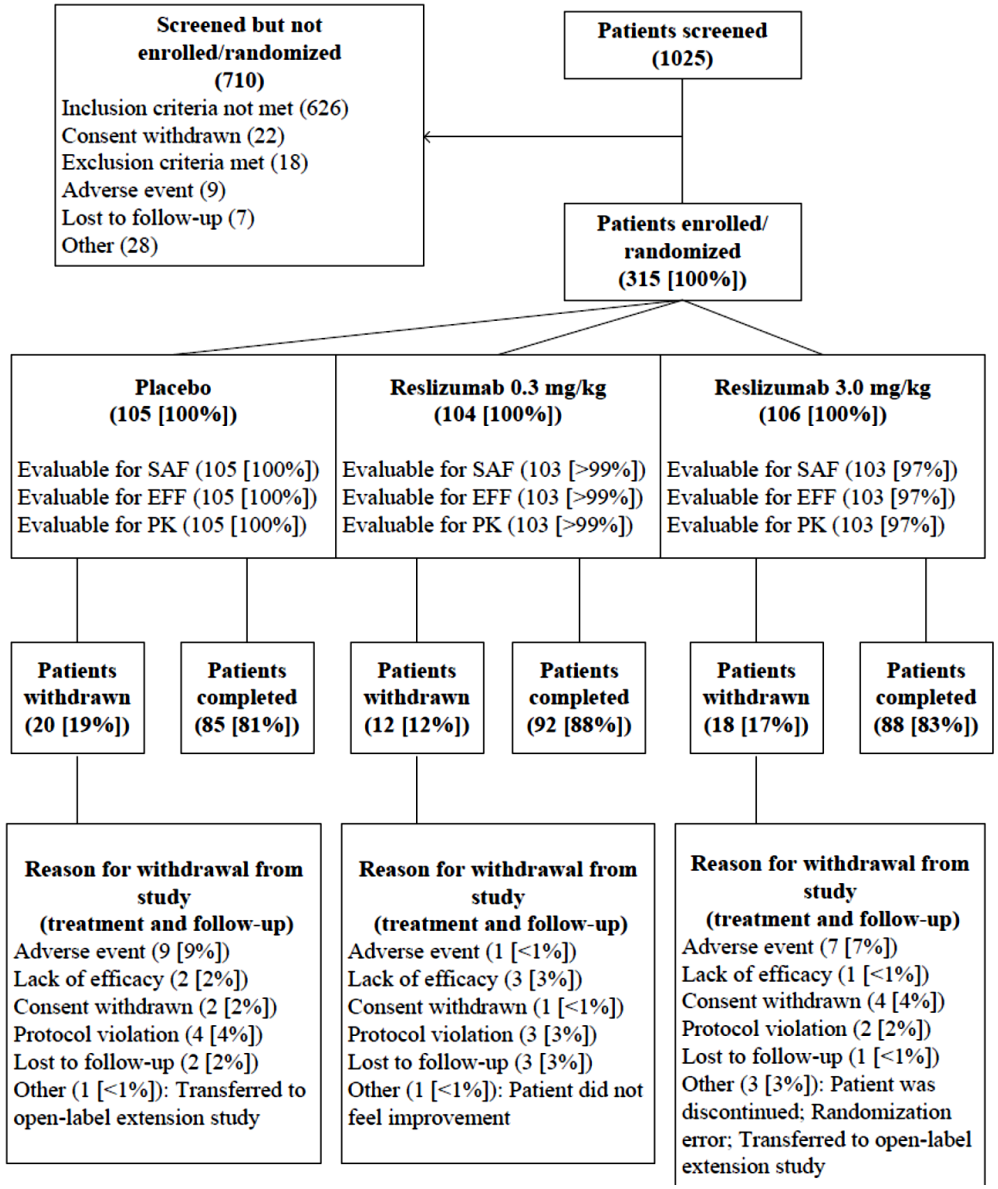
Abbreviations: FEV_1, forced expiratory volume in one second.

4.5.1.3 C38072/3081

A total of 315 patients (randomised set) were randomly assigned to treatment (104 in the reslizumab 0.3 mg/kg group, 106 in the reslizumab 3.0 mg/kg group and 105 in the placebo group). Four patients were withdrawn before receiving any study drug (1 in the reslizumab 0.3 mg/kg group [did not meet inclusion criteria] and 3 in the reslizumab 3.0 mg/kg group [2 withdrew consent and 1 was incorrectly randomised]); 311 (99%) patients received at least one dose of study drug and were included in the FAS.

Of the 315 randomised patients, 265 (84%) completed the study. The most common reason for study discontinuation was AEs, (1 [<1%] patient in the reslizumab 0.3 mg/kg group, 7 [7%] patients in the reslizumab 3.0 mg/kg group, and 9 [9%] patients in the placebo group). A CONSORT diagram for C38072/3081 is presented in Figure 4.

Figure 4: CONSORT diagram for C38072/3081



Abbreviations: EFF, efficacy; PK, pharmacokinetics; SAF, safety.

4.5.2 *Baseline demographics and disease-specific characteristics*

Patient demographics at baseline were generally similar across C38072/3082, C38072/3083 and C38072/3081. More female subjects than male subjects were enrolled in each trial (Table 17). In all three trials the treatment groups were well balanced with regard to age, race, ethnicity, body weight, height and body mass index (BMI). In C38072/3083 and C38072/3081 the treatment groups were well balanced with regard to sex; in C38072/3082 the proportion of patients who were male was larger in the reslizumab group (42%) than the placebo group (34%).

Baseline disease-specific characteristics were generally similar for each of the RCTs (Table 18). Overall, patients in C38072/3082 had a slightly lower % predicted FEV_1 than patients in C38072/3083 and C38072/3081. More patients in C38072/3082 were using oral corticosteroids at baseline compared with C38072/3083 (use of systemic, including oral, corticosteroids was an exclusion criteria in C38073/3081). Patients in C38072/3081 reported slightly lower daily average beta-agonist use compared with those in the other two trials. Patients were required to have had ≥1 asthma exacerbation in the 12 months prior to screening to be eligible for C38072/3082 and C38072/3083. Asthma exacerbation was not an inclusion criteria in C38072/3081; in this trial more than half of patients in each treatment group had experienced an exacerbation in the previous 12 months.

In all three trials, baseline disease-specific characteristics were generally similar between the reslizumab and placebo groups, and were indicative of a population with inadequately-controlled, moderate to severe asthma with elevated blood eosinophils.

Table 17: Baseline demographics of participants in the RCTs across randomised groups – randomised set

Baseline demographic	C38072/3082		C38072/3083		C38072/3081		
	Reslizumab 3.0 mg/kg N=245	Placebo N=244	Reslizumab 3.0 mg/kg N=232	Placebo N=232	Reslizumab 0.3 mg/kg N=104	Reslizumab 3.0 mg/kg N=106	Placebo N=105
Age, years							
n	245	244	232	232	104	106	105
Mean (SD)	46.6 (13.82)	46.7 (14.83)	46.4 (13.79)	47.5 (13.75)	44.5 (14.03)	43.0 (14.41)	44.2 (14.89)
Gender							
Male, n (%)	103 (42)	83 (34)	88 (38)	82 (35)	45 (43)	44 (42)	43 (41)
Female, n (%)	142 (58)	161 (66)	144 (62)	150 (65)	59 (57)	62 (58)	62 (59)
Race, n (%)							
White	173 (71)	182 (75)	168 (72)	169 (73)	80 (77)	90 (85)	85 (81)
Black	14 (6)	20 (8)	6 (3)	4 (2)	6 (6)	5 (5)	7 (7)
Asian	50 (20)	33 (14)	16 (7)	21 (9)	2 (2)	2 (2)	0
American Indian/ Alaskan Native	0	0	7 (3)	4 (2)	0	0	1 (<1)
Pacific Islander	1 (<1)	0	0	1 (<1)	0	0	1 (<1)
Other	7 (3)	9 (4)	35 (15)	33 (14)	16 (15)	9 (8)	11 (10)
Ethnicity, n (%)							
Hispanic/Latino	28 (11)	21 (9)	54 (23)	53 (23)	29 (28)	31 (29)	29 (28)
Non-Hispanic/ non-Latino	216 (88)	223 (91)	177 (76)	178 (77)	73 (70)	75 (71)	74 (70)
Unknown	1 (<1)	0	1 (<1)	1 (<1)	2 (2)	0	2 (2)

Baseline demographic	C38072/3082		C38072/3083		C38072/3081		
Weight, kg							
n	245	244	232	232	104	106	105
Mean (SD)	75.6 (19.05)	76.5 (18.71)	74.7 (15.72)	73.9 (15.93)	75.9 (18.80)	75.7 (20.30)	77.0 (20.10)
Height, cm							
n	245	242	232	232	104	106	105
Mean (SD)	164.9 (10.42)	165.0 (9.74)	166.4 (9.56)	165.2 (9.81)	166.2 (12.21)	165.9 (10.24)	166.4 (10.93)
BMI, kg/m^2							
n	245	242	232	232	104	106	105
Mean (SD)	27.7 (6.26)	28.0 (6.16)	27.0 (5.26)	27.0 (5.05)	27.6 (6.68)	27.4 (6.87)	27.7 (6.01)

Abbreviations: BMI, body mass index; RCT, randomised controlled trial; RS, randomised set; SD, standard deviation. Patient numbers (n) indicate patients for whom data were available.

Table 18: Disease-specific characteristics of participants in the RCTs – randomised set

Baseline characteristic	C38072/3082		C38072/3083		C38072/3081		
	Reslizumab 3.0 mg/kg N=245	Placebo N=244	Reslizumab 3.0 mg/kg N=232	Placebo N=232	Reslizumab 0.3 mg/kg N=104	Reslizumab 3.0 mg/kg N=106	Placebo N=105
Years since asthma diagnosis							
n	233	234	232	231	103	100	105
Mean (SD)	19.7 (15.19)	18.8 (14.2)	18.2 (14.43)	18.7 (13.28)	20.0 (15.23)	20.4 (15.64)	20.7 (14.49)
No. of patients experiencing asthma exacerbations in previous 12 months[†]							
Yes, n (%)	242 (99)	242 (99)	231 (<99)	232 (100)	58 (56)[‡]	60 (57)[‡]	57 (54)[‡]
No. of exacerbations in previous 12 months							
n	242	242	231	232	58	60	57
Mean (SD)	1.9 (1.63)	2.1 (2.31)	1.9 (1.58)	2.0 (1.78)	2.0 (1.68)	2.1 (1.63)	2.0 (1.27)
Months since last exacerbation							
n	242	241	232	232	57	58	57
Mean (SD)	5.2 (3.11)	5.3 (3.26)	5.8 (3.28)	5.3 (2.82)	4.8 (3.12)	5.0 (3.06)	4.7 (2.81)
History of allergy and/or nasal polyps, n (%)							
Chronic sinusitis	58 (24)	63 (26)	65 (28)	66 (28)	24 (23)	25 (24)	16 (15)
Atopic dermatitis	25 (10)	31 (13)	24 (10)	19 (8)	10 (10)	12 (11)	15 (14)
Aspirin sensitivity	20 (8)	19 (8)	28 (12)	36 (16)	13 (13)	15 (14)	9 (9)
Allergic rhinitis	141 (58)	145 (59)	129 (56)	144 (62)	65 (63)	79 (75)	72 (69)
Allergy shots	18 (7)	22 (9)	18 (8)	18 (8)	14 (13)	15 (14)	15 (14)

Baseline characteristic	C38072/3082		C38072/3083		C38072/3081		
Eosinophilic oesophagitis	2 (<1)	0	1 (<1)	0	1 (<1)	1 (<1)	0
Eosinophilic gastroenteritis	1 (<1)	1 (<1)	0	1 (<1)	0	0	0
Nasal polyps	65 (27)	62 (25)	56 (24)	62 (27)	27 (26)	30 (28)	24 (23)
Airway reversibility, %							
n	245	244	232	232	104	106	105
Mean (SD)	26.1 (15.47)	26.3 (18.10)	28.1 (16.06)	28.7 (23.75)	24.2 (13.62)	26.2 (18.63)	25.4 (15.62)
FEV_1, L							
n	245	244	232	232	103	105	105
Mean (SD)	1.894 (0.7258)	1.928 (0.7908)	2.129 (0.7848)	2.004 (0.6682)	2.157 (0.8506)	2.192 (0.7923)	2.222 (0.8125)
% predicted FEV_1							
n	245	244	232	232	103	105	105
Mean (SD)	63.6 (18.55)	65.0 (19.80)	70.4 (20.98)	68.0 (18.93)	68.8 (18.48)	70.4 (18.43)	71.1 (19.84)
FVC, L							
n	245	244	232	232	103	105	105
Mean (SD)	2.959 (0.9628)	3.015 (1.1298)	3.187 (1.0471)	3.000 (0.9148)	3.289 (1.1232)	3.220 (1.0114)	3.288 (1.0503)
$FEF_{25–75\%}$, L/second							
n	240	241	231	231	103	105	105
Mean (SD)	1.259 (0.8094)	1.567 (3.8223)	1.508 (0.8829)	1.860 (6.9954)	2.337 (8.9642)	1.731 (1.5370)	1.657 (0.9201)
ACQ overall score							
n	245	244	232	232	104	106	105
Mean (SD)	2.657 (0.8541)	2.763 (0.8782)	2.570 (0.89)	2.605 (0.79)	2.481 (0.9059)	2.590 (0.9108)	2.471 (0.8301)
AQLQ overall score							

Baseline characteristic	C38072/3082		C38072/3083		C38072/3081		
n	243	242	229	231	103	105	105
Mean (SD)	4.303 (1.1208)	4.159 (1.0883)	4.352 (1.0220)	4.223 (1.0794)	4.501 (1.2402)	4.175 (1.2297)	4.374 (1.2047)
ASUI overall score							
n	241	241	228	229	104	106	105
Mean (SD)	0.633 (0.1938)	0.613 (0.2029)	0.664 (0.2005)	0.649 (0.1919)	0.675 (0.2052)	0.655 (0.1945)	0.674 (0.1897)
Blood eosinophil count[§], cells/µL							
n	245	244	232	232	104	106	105
Mean (SD)	696 (767.7)	624 (590.3)	610 (411.5)	688 (682.4)	648 (491.7)	592 (387.8)	601 (433.1)
Total daily dose of ICS, µg							
n	240	241	229	231	102	105	105
Mean (SD)	824.1 (380.28)	847.7 (442.13)	856.0 (588.40)	756.9 (274.23)	756.3 (308.57)	813.5 (452.74)	756.7 (370.59)
Oral corticosteroid use							
Yes, n (%)	46 (19)	46 (19)	27 (12)	27 (12)	0	0	0
SABA use in past 3 days							
Yes, n (%)	170 (69)	188 (77)	182 (78)	181 (78)	72 (69)	78 (74)	81 (77)
Daily average no. of SABA puffs[††]							
n	242	241	204	201	104	106	104
Mean (SD)	2.4 (2.82)	2.7 (3.18)	2.9 (2.82)	2.7 (2.41)	1.9 (2.44)	2.2 (2.56)	2.3 (2.20)

Abbreviations: ACQ, Asthma Control Questionnaire; ASUI, Asthma Symptom Utility Index; AQLQ, Asthma Quality of Life Questionnaire; $FEF_{25–75\%}$, 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; RCT, randomised controlled trial; SABA, short-acting beta-agonist; SD, standard deviation. Data were missing for some patients, as indicated by patient numbers in the table.
[†]In C38072/3082 and C38072/3083, asthma exacerbations were defined as investigator-determined exacerbations requiring oral, intramuscular or intravenous corticosteroids for ≥3 days in the 12 months prior to screening. In C38072/3081, asthma exacerbations were defined as any of the following: 1) A ≥20% reduction in FEV_1, 2) Hospitalisation because of asthma, 3) Emergency treatment because of asthma, or 4) Use of prednisone or systemic corticosteroids for ≥3 days. [‡]CRF data. [§]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. ††Based on patient-reported number of puffs over the past 3 days.

4.6 *Quality assessment of the relevant randomised controlled trials*

A quality assessment for the pivotal RCTs 3082, 3083 and 3081 is provided in Table 19. This table also contains a quality assessment for the supportive study 3084 (summarised in Section 4.7.4).

A complete quality assessment for each RCT is provided in Appendix 2.

Table 19: Quality assessment results for parallel group RCTs

Study question	Study 3082	Study 3083	Study 3081	Study 3084
Was randomisation carried out appropriately?	Yes	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Yes	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes	Yes

Abbreviations: RCT, randomised controlled trial.

4.7 *Clinical effectiveness results of the relevant randomised controlled trials*

4.7.1 *C38072/3082*

4.7.1.1 Primary efficacy outcome: Frequency of CAEs

Treatment with reslizumab led to a statistically significant reduction from baseline in CAE frequency compared with placebo (p<0.0001). The frequency of adjudicated CAE events (reported by the investigator and confirmed by committee) during the 52-week treatment period was 0.72±1.22 in the reslizumab group and 1.34±1.76 with placebo (Table 20).

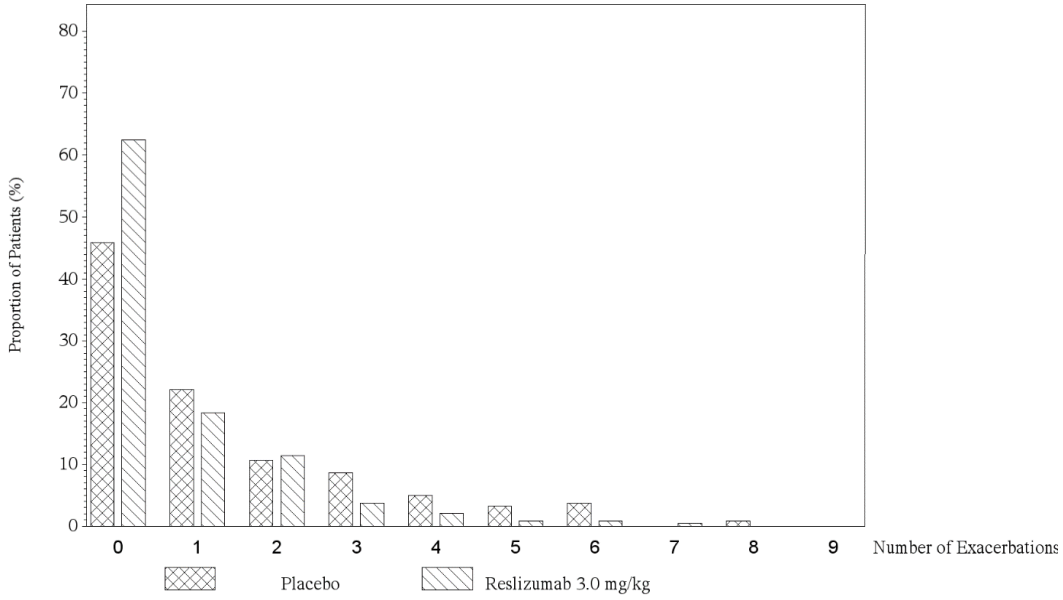
The frequency distribution of CAEs is shown in Figure 5; the percentage of patients with one or more CAEs was generally lower in the reslizumab group than in the placebo group across this distribution. The majority (62%) of patients treated with reslizumab experienced no CAEs, compared with 46% of patients treated with placebo.

Table 20: CAE frequency during the 52-week treatment period – randomised set (adjudicated data)

	Reslizumab 3.0 mg/kg N=245	**Placebo N=244**
Patients with ≥1 CAE, n (%)	92 (37.6)	132 (54.1)
CAE frequency during treatment period, mean (SD)	0.72 (1.22)	1.34 (1.76)
Adjusted CAE rate, mean (95% CI)	0.90 (0.68; 1.20)	1.80 (1.37; 2.37)
CAE rate ratio (95% CI), reslizumab vs placebo	0.50 (0.37; 0.67)	
p-value	<0.0001	

Abbreviations: CAE, clinical asthma exacerbation; CI, confidence interval; SD, standard deviation.

Figure 5: CAEs per patient during the 52-week treatment period – randomised set (adjudicated data)



Abbreviations: CAE, clinical asthma exacerbation.

Sensitivity analyses of the primary outcome

The results of sensitivity analyses using 1) an offset variable that did not exclude the summed duration of CAEs from the follow-up time, 2) a multiple imputation method (104) for missing data, and 3) both imputing missing data and without excluding duration of asthma exacerbations from the offset, are presented in Table 21.

All sensitivity analyses demonstrated a significantly lower frequency of adjudicated CAEs in the reslizumab versus placebo group, with similar results to the primary efficacy analysis. Thus, neither excluding the summed duration of CAEs, or any potential bias favouring reslizumab introduced by missing data, had a notable effect on the results of the primary efficacy analysis.

Table 21: Sensitivity analyses of the primary efficacy outcome

Sensitivity analysis	**Reslizumab 3.0 mg/kg N=245**	**Placebo N=244**
Analysis using offset variable that did not exclude summed duration of CAEs from follow-up time		
Adjusted CAE rate, mean (95% CI)	0.82 (0.63; 1.06)	1.51 (1.18; 1.95)
CAE rate ratio (95% CI), reslizumab vs placebo	0.54 (0.41; 0.71)	
p-value	<0.0001	
Analysis using multiple imputation method for missing data		
Adjusted CAE rate, mean (95% CI)	0.91 (0.65; 1.26)	1.75 (1.29; 2.38)
CAE rate ratio (95% CI), reslizumab vs placebo	0.52 (0.38; 0.69)	
p-value	<0.0001	
Analysis using both offset variable that did not exclude summed duration of CAEs from follow-up time and multiple imputation method for missing data		
Adjusted CAE rate, mean (95% CI)	0.83 (0.61; 1.12)	1.53 (1.15; 2.02)
CAE rate ratio (95% CI), reslizumab vs placebo	0.54 (0.41; 0.71)	
p-value	<0.0001	

Abbreviations: CAE, clinical asthma exacerbation; CI, confidence interval.

4.7.1.2 Secondary analysis of the primary outcome measure

Adjudicated CAEs by type of medical intervention

The analysis of CAE frequency by the type of medical intervention used to treat the event is presented in Table 22. The most common intervention in both the reslizumab and placebo groups was treatment with a systemic corticosteroid (80/92 [87%] and 118/132 [89%] patients, respectively), most commonly administered orally (77/80 [96%] and 117/118 [99%] patients, respectively). The efficacy of reslizumab in reducing the frequency of CAEs in these two major patient subsets, versus placebo, was consistent with the results of the primary efficacy analysis.

Few patients required hospitalisation and/or an emergency room visit due to a CAE; the adjusted rate of these events was lower with reslizumab versus placebo but the difference was not statistically significant.

Table 22: CAE frequency during the 52-week treatment period by type of medical intervention – randomised set (adjudicated data)

Medical intervention	Reslizumab 3.0 mg/kg N=245	Placebo N=244
Patients with ≥1 CAE, n (%)	92 (37.6)	132 (54.1)
CAEs requiring systemic corticosteroids for ≥3 days		
Patients with ≥1 CAE, n (%)	80 (32.7)	118 (48.4)
CAE frequency during treatment period, mean (SD)	0.55 (1.05)	1.12 (1.61)
Adjusted CAE rate, mean (95% CI)	0.72 (0.53; 0.99)	1.60 (1.20; 2.15)
CAE rate ratio (95% CI), reslizumab vs placebo	0.45 (0.33; 0.62)	
p-value[†]	<0.0001	
CAEs requiring oral corticosteroids for ≥3 days		
Patients with ≥1 CAE, n (%)	77 (31.4)	117 (48.0)
CAE frequency during treatment period, mean (SD)	0.53 (1.02)	1.09 (1.59)
Adjusted CAE rate, mean (95% CI)	0.70 (0.51; 0.96)	1.59 (1.18; 2.14)
CAE rate ratio (95% CI), reslizumab vs placebo	0.44 (0.32; 0.61)	
p-value	<0.0001	
CAEs requiring hospitalisation		
Patients with ≥1 CAE, n (%)	9 (3.7)	11 (4.5)
CAE frequency during treatment period, mean (SD)	0.04 (0.19)	0.09 (0.51)
CAEs requiring an emergency room visit		
Patients with ≥1 CAE, n (%)	13 (5.3)	12 (4.9)
CAE frequency during treatment period, mean (SD)	0.07 (0.29)	0.08 (0.38)
CAEs requiring hospitalisation and/or an emergency room visit		
Patients with ≥1 CAE, n (%)	22 (9.0)	21 (8.6)
CAE frequency during treatment period, mean (SD)	0.10 (0.34)	0.17 (0.72)
Adjusted CAE rate, mean (95% CI)	0.14 (0.07; 0.27)	0.21 (0.11; 0.40)
CAE rate ratio (95% CI), reslizumab vs placebo	0.66 (0.32; 1.36)	
p-value	0.2572	

Abbreviations: CAE, clinical asthma exacerbation; CI, confidence interval; SD, standard deviation.
[†]The analysis of overall change from baseline in SABA use over 16 weeks (a secondary efficacy outcome; see Section 4.7.1.8) failed to show statistical significance; hence the Type 1 error rate for analysis of CAEs treated with systemic corticosteroids was not controlled for multiple comparisons and the p-value is nominal.

Investigator-determined CAEs

The frequency of investigator-determined CAEs was analysed separately from CAEs identified by the adjudication committee. The results were similar to those obtained using the adjudicated data set; there was a significant reduction in CAE frequency with reslizumab compared with placebo (adjusted CAE rates were 1.08 and 2.00, respectively; rate ratio of 0.54 [95% confidence interval (CI): 0.40; 0.73]; nominal p<0.0001). The results of sensitivity analysis using an offset variable that did not exclude the summed duration of CAEs from the follow-up time were consistent with the primary analysis of investigator-determined CAEs.

4.7.1.3 Secondary efficacy outcome: Change from baseline in FEV_1

A significantly greater improvement (increase) in FEV_1 was observed with reslizumab compared with placebo for both the change from baseline to Week 16 and the overall change from baseline over 16 weeks (Table 23). Although not controlled for multiple comparisons, treatment effects were also observed for the overall change over 52 weeks and at endpoint (nominal p-values were p<0.0001 and p=0.0003, respectively).

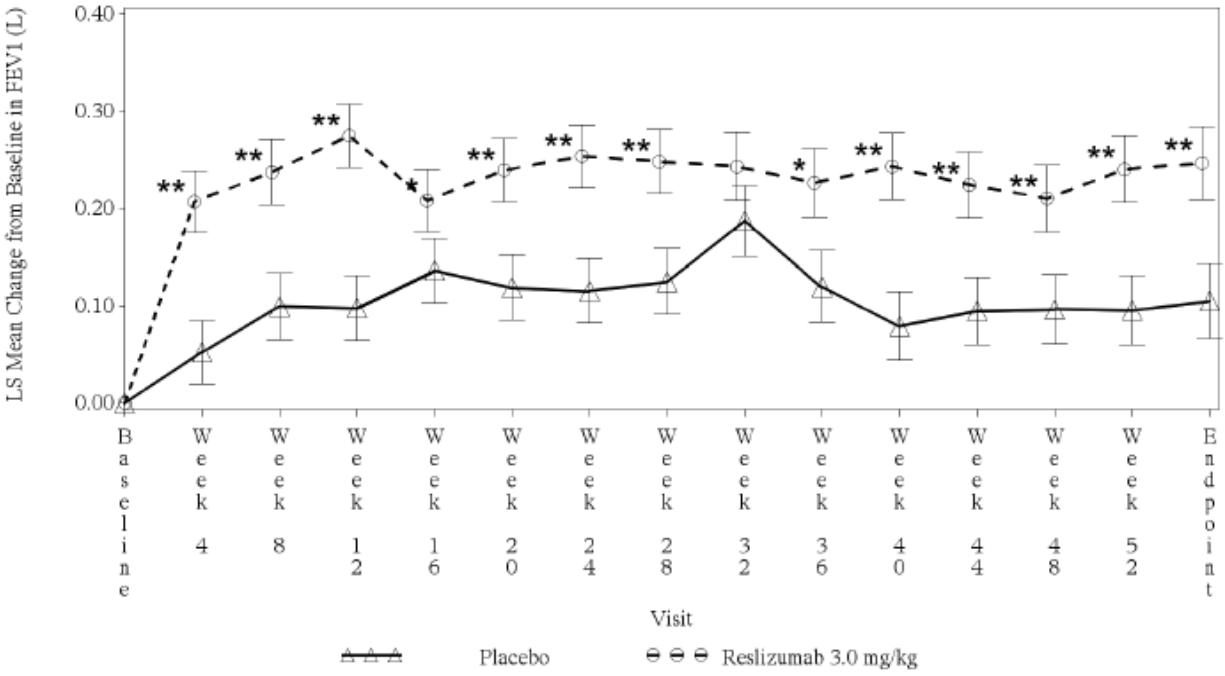
Table 23: Change from baseline in FEV_1 – randomised set

	Reslizumab 3.0 mg/kg N=245	**Placebo N=244**
Baseline FEV_1, L		
n	245	244
Mean (SD)	1.89 (0.73)	1.93 (0.79)
Change in FEV_1 to Week 16, L		
n	232	228
Mean (SD)	0.20 (0.42)	0.13 (0.38)
LS mean (SE)	0.21 (0.03)	0.14 (0.03)
Treatment difference (SE), reslizumab – placebo	0.07 (0.04)	
95% CI	0.001; 0.14	
p-value	0.0483	
Change in FEV_1 over 16 weeks, L		
n	243	241
LS mean (SE)	0.25 (0.03)	0.11 (0.03)
Treatment difference (SE), reslizumab – placebo	0.14 (0.03)	
95% CI	0.08; 0.20	
p-value	<0.0001	

Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in one second; L, litres; LS, least squares; SD, standard deviation; SE, standard error.

Change in FEV_1 from baseline to Weeks 4, 8, 12, 20, 24, 28, 32, 36, 40, 44, 48 and 52 (analysed as an 'other' efficacy outcome) is presented in Figure 6. A greater improvement in FEV_1 was observed with reslizumab versus placebo at the first assessment visit (Week 4) and at most subsequent visits.

Figure 6: Change from baseline in FEV_1 to each visit and endpoint – randomised set



Abbreviations: FEV_1, forced expiratory volume in one second; LS, least squares.
*Nominal p≤0.05 and **nominal p≤0.005; p-values were not adjusted to control for multiplicity. Data are LS means±SE.

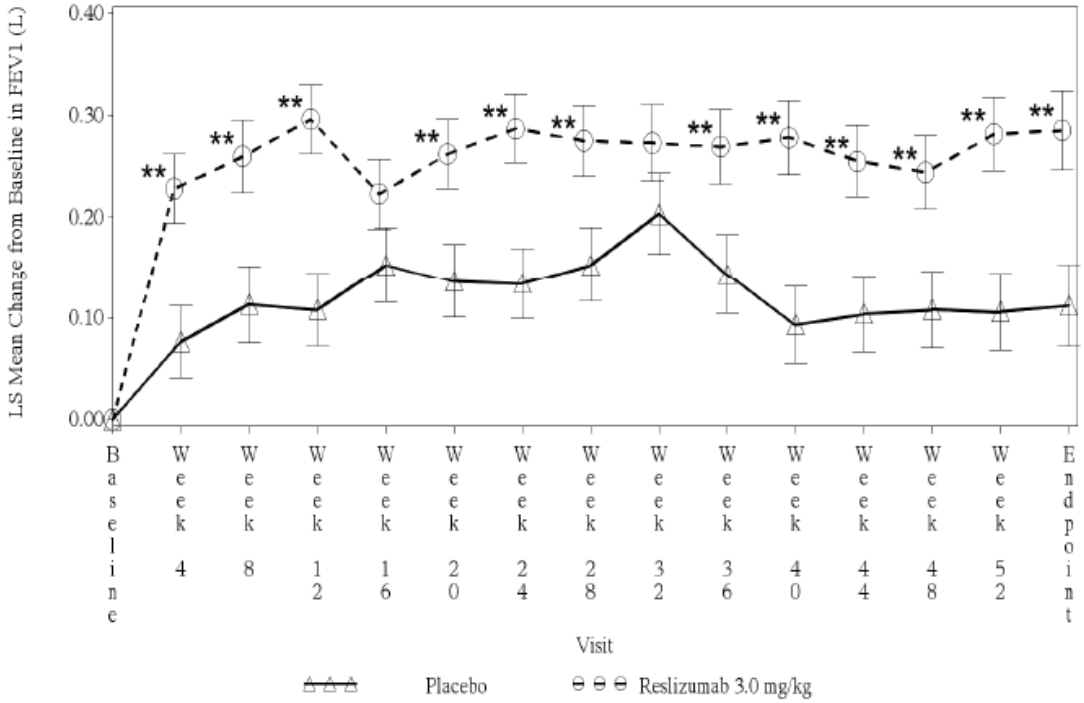
FEV_1 analysis set

The change from baseline in FEV_1 was also analysed in the subpopulation of patients with a baseline % predicted FEV_1 value of ≤85% (the FEV_1 analysis set). This more severe subgroup was comprised of the majority of patients in both the reslizumab and placebo groups (218/244 [89%] and 205/244 [84%] patients, respectively). The least squares (LS) mean change from baseline was:

- numerically greater with reslizumab versus placebo to Week 16 (0.22 L versus 0.15 L; treatment difference 0.07 [95% CI: –0.01; 0.15]; nominal p=0.0834)
- significantly greater with reslizumab versus placebo over 16 weeks (0.27 L versus 0.13 L; treatment difference 0.14 [95% CI: 0.07; 0.21]; nominal p<0.0001).

Similar to the analysis using the randomised set, a greater improvement in FEV_1 was observed with reslizumab versus placebo at Week 4 and throughout the study in the FEV_1 analysis set (Figure 7).

Figure 7: Change from baseline in FEV_1 to each visit and endpoint – FEV_1 analysis set



Abbreviations: FEV_1, forced expiratory volume in one second.
**Nominal p≤0.005; p-values were not adjusted to control for multiplicity. Data are LS means ± SE.

4.7.1.4 Secondary efficacy outcome: Change from baseline in AQLQ score

There was a significantly greater improvement (increase) in AQLQ total score from baseline to Week 16 in the reslizumab group compared with the placebo group (Table 24). Although not controlled for multiplicity of testing, greater improvements in AQLQ score were also seen with reslizumab versus placebo over 52 weeks and at endpoint (nominal p=0.0004 and nominal p=0.0002, respectively).

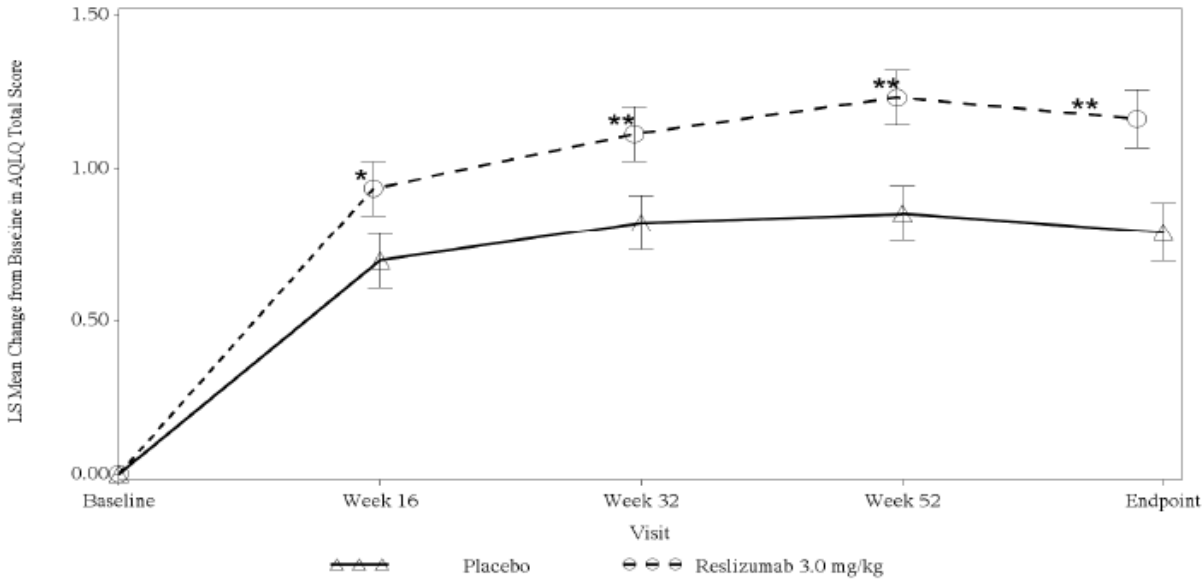
Table 24: Change from baseline in AQLQ total score – randomised set

	Reslizumab 3.0 mg/kg N=245	**Placebo N=244**
Baseline AQLQ total score		
n	243	242
Mean (SD)	4.30 (1.12)	4.16 (1.09)
Change in AQLQ total score to Week 16		
n	228	229
Mean (SD)	1.03 (1.19)	0.87 (1.15)
LS mean (SE)	0.93 (0.09)	0.70 (0.09)
Treatment difference (SE), reslizumab – placebo	0.24 (0.10)	
95% CI	0.05; 0.43	
p-value	0.0143	

Abbreviations: AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; LS, least squares; SD, standard deviation; SE, standard error.

Change in AQLQ total score from baseline to Weeks 32 and 52 was analysed as an 'other' efficacy outcome. The greater improvement observed with reslizumab at Week 16 was sustained at both timepoints (Figure 8). A similar treatment effect was also observed when the change from baseline in AQLQ score for each of the four domains (symptoms, activity limitation, emotional function and environmental stimuli) was analysed at Weeks 16 and 52 (not shown).

Figure 8: Change from baseline in AQLQ total score to each visit and endpoint – randomised set



Abbreviations: AQLQ, Asthma Quality of Life Questionnaire.
*Nominal p≤0.05 and **nominal p≤0.005; p-values were not adjusted to control for multiplicity. Data are LS means ± SE.

AQLQ responders

The proportion of patients achieving at least a 0.5-point improvement in AQLQ total score was significantly greater with reslizumab than with placebo at Week 52 (***[redacted]; [redacted]% vs [redacted]%; nominal p=[redacted]); numerically greater improvements were observed at Weeks 16 and 32. A greater proportion of responders was also observed with reslizumab versus placebo for each of the four AQLQ domain scores at Weeks 16, 32 and 52 (not shown).

Abbreviations: AQLQ, Asthma Quality of Life Questionnaire; U, unit.
*Nominal p≤0.05; p-value was not adjusted to control for multiplicity.

4.7.1.5 Secondary efficacy outcome: Change from baseline in ACQ score

Analysis of the overall change in ACQ total score over 16 weeks demonstrated a significantly greater improvement (decrease) for patients in the reslizumab group compared with the placebo group (Table 25). Although not controlled for multiplicity of testing, a treatment effect was also seen from baseline to Week 16, over 52 weeks and at endpoint (nominal p-values were 0.0439, 0.0002 and 0.0003, respectively.

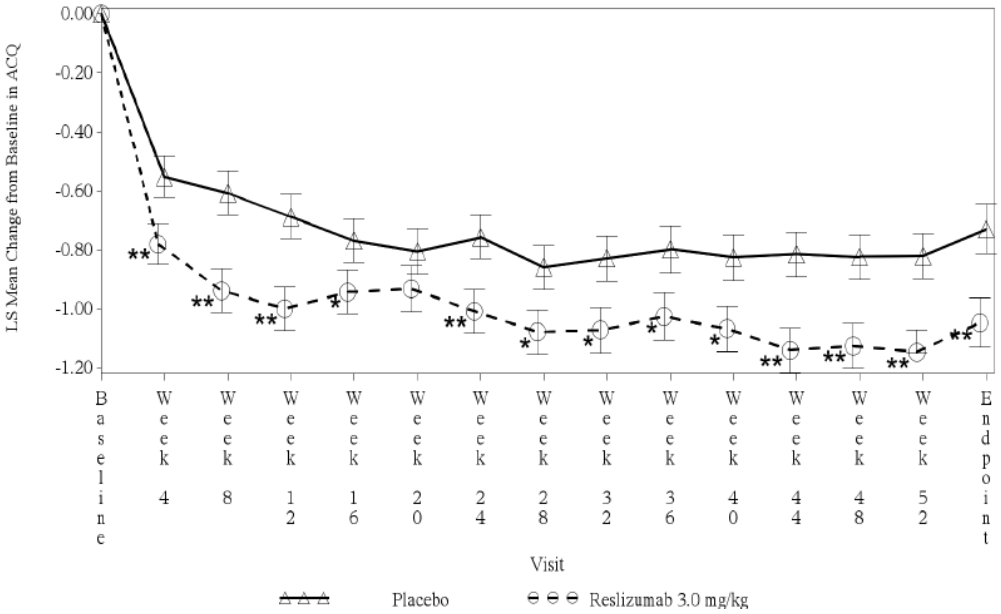
Change from baseline in ACQ total score from baseline to each treatment visit is presented in Figure 9 (analysed as an 'other' efficacy outcome); a greater improvement was observed with reslizumab versus placebo at the first 4-week assessment visit (Week 4) and throughout the study.

Table 25: Change from baseline in ACQ total score – randomised set

	Reslizumab 3.0 mg/kg N=245	**Placebo N=244**
Baseline ACQ total score		
n	245	244
Mean (SD)	2.66 (0.85)	2.76 (0.88)
Change in ACQ total score over 16 weeks		
n	242	241
LS mean (SE)	–0.94 (0.07)	–0.68 (0.07)
Treatment difference (SE), reslizumab – placebo	–0.27 (0.07)	
95% CI	–0.40; –0.13	
p-value	0.0001	

Abbreviations: ACQ, Asthma Control Questionnaire; CI, confidence interval; LS, least squares; SD, standard deviation; SE, standard error.

Figure 9: Change from baseline in ACQ total score to each visit and endpoint – randomised set



Abbreviations: ACQ, Asthma Control Questionnaire; LS, least squares; U, unit.
*Nominal p≤0.05 and **nominal p≤0.005; p-values were not adjusted to control for multiplicity.

ACQ responders

The proportion of patients achieving at least a 0.5-point improvement in ACQ total score was greater with reslizumab versus placebo at each treatment visit from Week 4 to Week 52 (***[redacted]); the proportion of responders at Week 52 was [redacted]% and [redacted]%, respectively (nominal p=[redacted]).

[redacted]

Abbreviations: ACQ, Asthma Control Questionnaire; U, unit.
*Nominal p≤0.05 and **nominal p≤0.005; p-values were not adjusted to control for multiplicity.

4.7.1.6 Secondary efficacy outcome: Time to first CAE

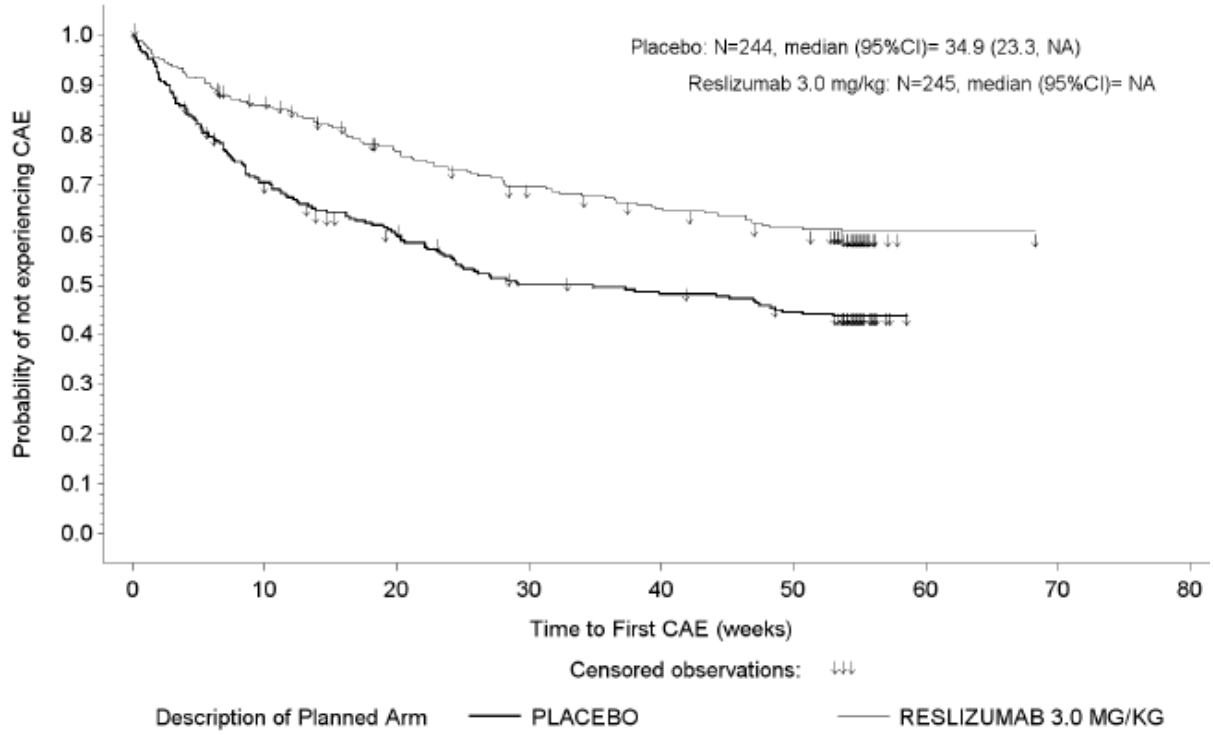
The probability of not experiencing a CAE by Week 52 was found to be significantly greater in the reslizumab versus placebo group (Table 26 and Figure 10). The median time to first CAE could not be estimated for the reslizumab group because less than 50% of patients in that group experienced ≥1 CAE (see Table 20).

Table 26: Time to first CAE – randomised set (adjudicated data)

	Reslizumab 3.0 mg/kg N=245	Placebo N=244
Kaplan-Meier estimate		
Quartile 1, weeks (95% CI)	22.3 (16.1; 31.3)	7.7 (5.7; 10.6)
Median, weeks (95% CI)	NA	34.9 (23.3; NA)
Quartile 3, weeks (95% CI)	NA	NA
Kaplan-Meier estimate of probability of not experiencing a CAE by Week 52		
% (95% CI)	61.3 (54.7; 67.2)	44.2 (37.7; 50.5)
Hazard ratio (95% CI), reslizumab vs placebo	0.58 (0.44; 0.75)	
p-value	<0.0001	

Abbreviations: CAE, clinical asthma exacerbation; CI, confidence interval; NA, not applicable.

Figure 10: Time to first CAE – randomised set (adjudicated data)



Abbreviations: CAE, clinical asthma exacerbation; CI, confidence interval; NA, not applicable.

Patients with CAEs requiring systemic corticosteroids

Time to first CAE was also analysed for the subgroup of patients who experienced a CAE that required treatment with systemic (primarily oral) corticosteroids. Similar results were observed for this subgroup as with all patients who experienced a CAE. The Kaplan-Meier estimate of probability of not experiencing a CAE requiring systemic corticosteroids by Week 52 was 65.9% (95% CI: 59.4; 71.6) with reslizumab and 49.6% (95% CI: 43.0; 55.9) with placebo (hazard ratio [reslizumab vs placebo] of 0.57 [95% CI: 0.43; 0.76], nominal p<0.0001).

4.7.1.7 Secondary efficacy outcome: Change from baseline in ASUI score

A significantly greater improvement (increase) in ASUI total score over 16 weeks was observed in the reslizumab group compared with the placebo group (Table 27). A treatment effect was also observed for the change from baseline to Week 16 (nominal p=0.0215), over 52 weeks (nominal p<0.0001), and at endpoint (nominal p<0.0001).

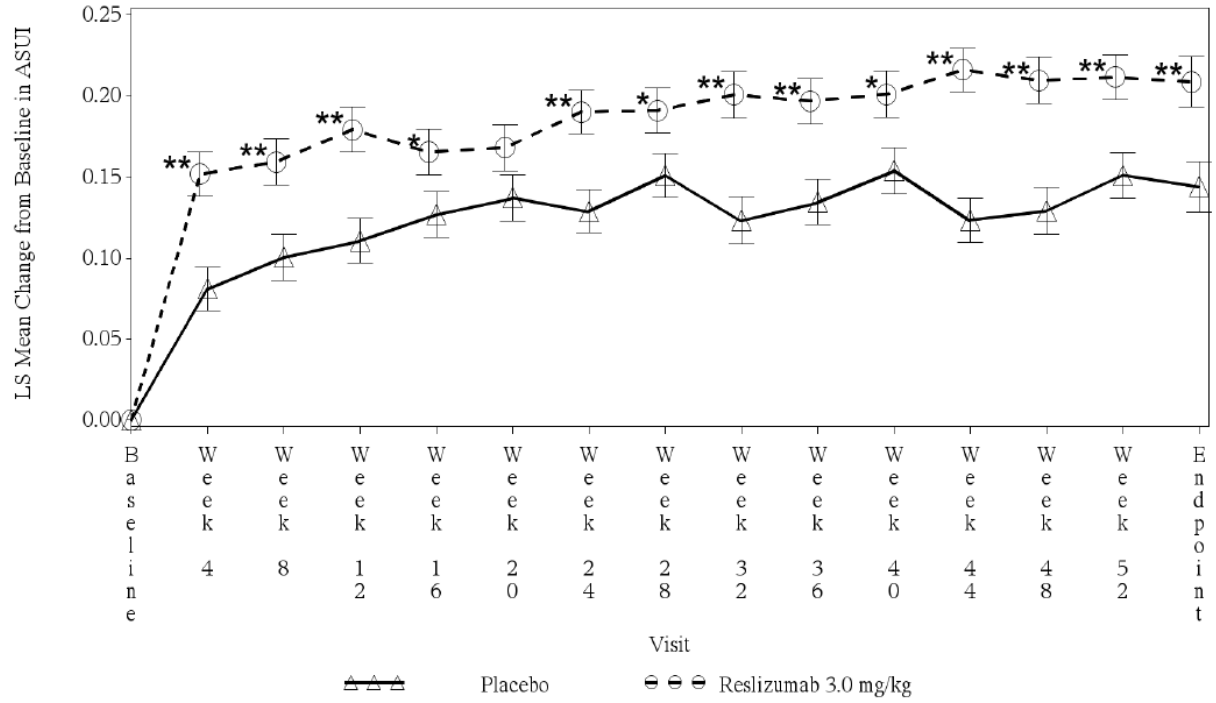
Change from baseline in ASUI total score to each treatment visit was analysed as an 'other' efficacy outcome (Figure 11); a greater improvement was observed in the reslizumab group than the placebo group at Week 4 and throughout the study.

Table 27: Change from baseline in ASUI score – randomised set

	Reslizumab 3.0 mg/kg N=245	**Placebo N=244**
Baseline ASUI total score		
n	241	241
Mean (SD)	0.63 (0.19)	0.61 (0.20)
Change in ASUI total score over 16 weeks		
n	238	238
LS mean (SE)	0.17 (0.01)	0.11 (0.01)
Treatment difference (SE), reslizumab – placebo	0.06 (0.01)	
95% CI	0.03; 0.08	
p-value	<0.0001	

Abbreviations: ASUI, Asthma Symptom Utility Index; CI, confidence interval; LS, least squares; SD, standard deviation; SE, standard error.

Figure 11: Change from baseline in ASUI score to each visit and endpoint – randomised set



Abbreviations: ASUI, Asthma Symptom Utility Index; LS, least squares.
*Nominal p≤0.05 and **nominal p≤0.005; p-values were not adjusted to control for multiplicity.

4.7.1.8 Secondary efficacy outcome: Change from baseline in SABA use

There was a numerically greater improvement (decrease in daily use) in the change in short-acting beta-agonist (SABA) use over 16 weeks in the reslizumab group compared with the placebo group, but the difference was not statistically significant (Table 28). Changes from baseline in daily use at Week 16, over 52 weeks and at endpoint were small and also not significantly different between groups. Change from baseline in daily SABA use to each treatment visit was analysed as an 'other' efficacy outcome. Although there was a general trend for a greater reduction in use with reslizumab versus placebo, the difference was not significant at any of the scheduled visits.

Table 28: Change from baseline in SABA use – randomised set

	Reslizumab 3.0 mg/kg N=245	**Placebo N=244**
Patients using SABA at baseline		
n	242	241
Yes, n (%)	170 (70)	188 (78)
Average SABA use at baseline		
n	242	241
Puffs/day, mean (SD)	2.4 (2.82)	2.7 (3.18)

	Reslizumab 3.0 mg/kg N=245	Placebo N=244
Change in SABA use (puffs/day) over 16 weeks		
n	240	238
LS mean (SE)	–0.64 (0.16)	–0.36 (0.16)
Treatment difference (SE), reslizumab – placebo	–0.28 (0.16)	
95% CI	–0.60; 0.05	
p-value	0.0919	

Abbreviations: CI, confidence interval; LS, least squares; SABA, short-acting beta-agonist; SD, standard deviation; SE, standard error.

4.7.1.9 Secondary efficacy outcome: Change from baseline in blood eosinophil count

There was a significantly greater decrease in blood eosinophil count over 16 weeks and 52 weeks in the reslizumab group compared with the placebo group (Table 29). A significant treatment difference was also observed for the change from baseline to Week 16 and at endpoint (nominal p<0.0001 for both).

Table 29: Change from baseline in blood eosinophil count – randomised set

	Reslizumab 3.0 mg/kg N=245	Placebo N=244
Baseline blood eosinophil count, cells/µL[†]		
n	245	244
Mean (SD)	696 (767.7)	624 (590.3)
Overall change in blood eosinophil count over 16 weeks[‡]**, cells/µL**		
n	243	241
LS mean (SE)	–584 (23.0)	–118 (23.2)
Treatment difference (SE), reslizumab – placebo	–0.466 (24.4)	
95% CI	–514; –418	
p-value	<0.0001	
Overall change in blood eosinophil count over 52 weeks[‡]**, cells/µL**		
n	243	241
LS mean (SE)	–582 (16.7)	–127 (16.8)
Treatment difference (SE), reslizumab – placebo	–455 (18.2)	
95% CI	–491; –419	
p-value	<0.0001	

Abbreviations: CI, confidence interval; LS, least squares; SD, standard deviation; SE, standard error.
[†]Patients were required to have a blood eosinophil count ≥400/µL at least once during the screening period; however, as this value did not necessarily occur at baseline, baseline eosinophil counts for the randomised set include some patients with values <400/µL. [‡]Because the results of the preceding secondary efficacy analysis (SABA use over 16 weeks) were not statistically significant, the analysis of change from baseline in blood eosinophil count over 16 and 52 weeks was not controlled for multiplicity.

Blood eosinophil count at each treatment visit was analysed as an 'other' efficacy outcome ([redacted]); a greater reduction was observed with reslizumab versus placebo at the first assessment visit and was sustained throughout the study. Of note, there was evidence of a treatment effect as early as 2–3 days after the first study drug infusion for patients at US centres who provided blood samples at these time points.

At the 90-day follow-up visit, blood eosinophil counts were available for only [redacted] patients in the reslizumab group and [redacted] patients in the placebo group, as the majority of patients enrolled in the open-label extension study C38072/3085. However, in this small cohort there was evidence of a partial return in blood eosinophil count (cells/µL) to a baseline level in patients treated with reslizumab (from a mean±SD of [redacted] at Week 52 to [redacted] at follow-up).

Horizontal bars indicate mean values.

4.7.1.10 Other efficacy outcomes

The analyses of change from baseline to specific visits in FEV_1, ASUI total score, ACQ total score, AQLQ total score, SABA use and blood eosinophil count are presented in Section 4.7.1.3 to Section 4.7.1.9 with the results of the relevant secondary efficacy variables. For the remaining analyses of lung function, no adjustments for multiplicity were applied and thus p-values are nominal. There were significantly greater improvements with reslizumab versus placebo for the outcomes listed below.

- **Change from baseline in forced vital capacity (FVC):**
  - over 16 weeks (treatment difference 0.13 L [95% CI: 0.05; 0.22], p=0.0011)
  - over 52 weeks (treatment difference 0.12 L [95% CI: 0.04; 0.20], p=0.0040)
  - at endpoint (treatment difference 0.12 L [95% CI: 0.03; 0.22], p=0.0112).

- **Change from baseline in % predicted FEV_1:**
  - over 16 weeks (treatment difference 4.2% [95% CI: 2.08; 6.25], p<0.0001)
  - over 52 weeks (treatment difference 3.9% [95% CI: 1.82; 5.96], p=0.0002)
  - at endpoint (treatment difference 4.6% [95% CI: 2.05; 7.09], p=0.0004).

There were no significant between-treatment differences for change in FVC to Week 16 or change in % predicted FEV_1 to Week 16. Numerically, but not significantly, greater improvements from baseline in forced expiratory flow at 25–75% forced vital capacity ($FEF_{25–75\%}$) were observed with reslizumab versus placebo to Week 16, over 16 and 52 weeks, and to endpoint.

4.7.1.11 Exploratory variables

Analyses of exploratory variables were not adjusted for multiplicity and thus p-values are nominal.

Sputum eosinophil count

Sputum samples were analysed for only [redacted] patients at baseline, precluding meaningful interpretation of any changes from baseline.

Change from baseline in PEFR

Peak expiratory flow rate (PEFR) data were available for [redacted]% of randomised patients in each group at baseline and approximately [redacted]% of patients at Week 52. There was a [redacted] with reslizumab versus placebo for the outcomes listed below.

- **Change from baseline in weekly average of daily morning PEFR:**
  - over 16 weeks (treatment difference [redacted] L/min [95% CI: 7.0; 31.1], p=[redacted])
  - over 52 weeks (treatment difference [redacted] L/min [95% CI: 6.7; 32.1], p=[redacted])
  - to Week 16 (treatment difference [redacted] L/min [95% CI: 3.7; 33.3], p=[redacted])
  - to endpoint (treatment difference [redacted] L/min [95% CI: 0.6; 31.9], p=[redacted]).
- **Change from baseline in weekly average of daily evening PEFR**
  - over 16 weeks (treatment difference [redacted] L/min [95% CI: 7.6; 31.9], p=[redacted])
  - over 52 weeks (treatment difference [redacted] L/min [95% CI: 7.1; 32.4], p=[redacted])
  - to Week 16 (treatment difference [redacted] L/min [95% CI: 2.9; 32.4], p=[redacted])
  - to endpoint (treatment difference [redacted] L/min [95% CI: 0.4; 31.8], p=[redacted]).

Fibulin-1

Fibulin-1 concentration was not measured due to the lack of a reliable assay.

Nasal polyps

Assessment of nasal polys was optional for adult patients at participating US centres. Results were analysed for only 24 patients at baseline and 17 patients at Week 52, precluding meaningful interpretation of any changes from baseline.

IgE

Mean serum IgE concentration was [redacted] in the reslizumab group ([redacted] µg/L) than the placebo group ([redacted] µg/L) at baseline and showed only a [redacted] in both groups

during the treatment period. The Week 52 change from baseline was [redacted] µg/L ([redacted]%) with reslizumab and [redacted] µg/L ([redacted]%) with placebo; interpretation of these small changes was not possible due to high data variability.

4.7.1.12 Efficacy conclusions

The primary efficacy results from C38072/3082 show that reslizumab 3.0 mg/kg, administered intravenously every 4 weeks over 52 weeks, is effective in controlling asthma exacerbations in patients with asthma and elevated blood eosinophils (≥400/µL) inadequately controlled by medium to high dose ICS.

Reslizumab treatment also improves lung function (FEV_1), asthma control (ACQ score), asthma symptoms (ASUI score) and asthma QoL (AQLQ score), and leads to a reduction in blood eosinophils consistent with the mechanism of action of this IL-5 monoclonal antibody.

4.7.2 *C38072/3083*

4.7.2.1 Primary efficacy outcome: Frequency of CAEs

Treatment with reslizumab led to a statistically significant reduction from baseline in CAE frequency compared with placebo (p<0.0001). The frequency of adjudicated CAE events (reported by the investigator and confirmed by committee) during the 52-week treatment period was 0.46±0.96 in the reslizumab group and 1.01±1.67 with placebo (Table 30).

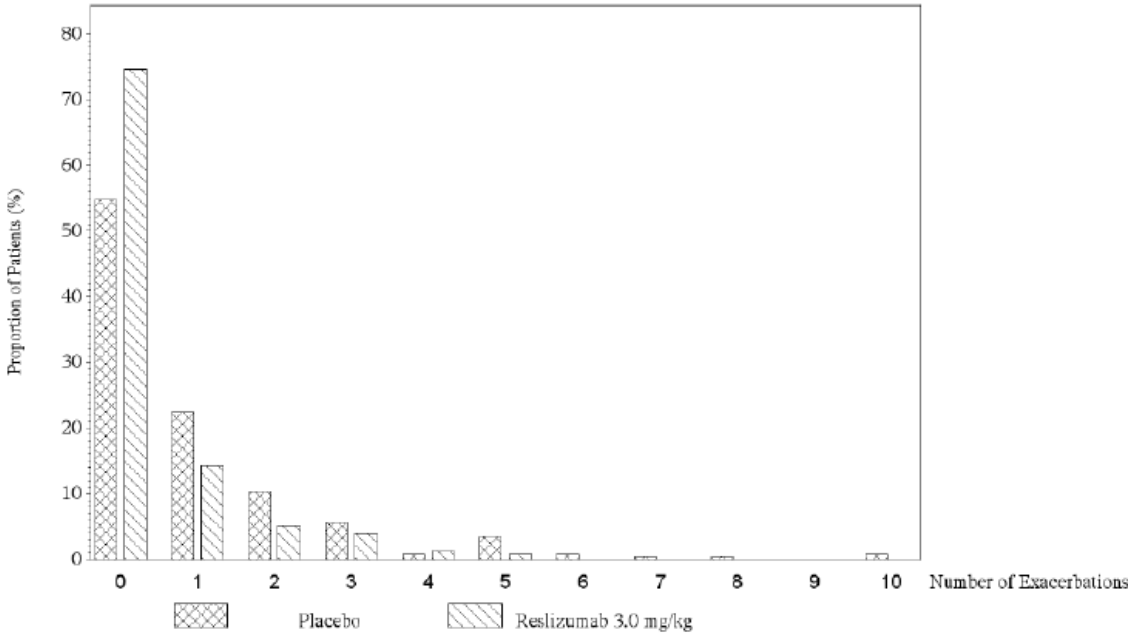
The frequency distribution of CAEs is shown in Figure 12; the percentage of patients with one or more CAEs was generally lower with reslizumab versus placebo across this distribution. The majority (75%) of patients treated with reslizumab experienced no CAEs, compared with 55% of patients treated with placebo.

Table 30: CAE frequency during the 52-week treatment period – randomised set (adjudicated data)

	Reslizumab 3.0 mg/kg N=232	**Placebo N=232**
Patients with ≥1 CAE, n (%)	59 (25.4)	105 (45.3)
CAE frequency during treatment period, mean (SD)	0.46 (0.96)	1.01 (1.67)
Adjusted CAE rate, mean (95% CI)	0.86 (0.55; 1.35)	2.11 (1.33; 3.36)
CAE rate ratio (95% CI), reslizumab vs placebo	0.41 (0.28; 0.59)	
p-value	<0.0001	

Abbreviations: CAE, clinical asthma exacerbation; CI, confidence interval; SD, standard deviation.

Figure 12: CAEs per patient during the 52-week treatment period – randomised set (adjudicated data)



Abbreviations: CAE, clinical asthma exacerbation.

Sensitivity analyses of the primary outcome

The results of sensitivity analyses using 1) an offset variable that did not exclude the summed duration of CAEs from the follow-up time, 2) a multiple imputation method (104) for missing data, and 3) both imputing missing data and without excluding duration of asthma exacerbations from the offset, are presented in Table 31.

All sensitivity analyses demonstrated a significantly lower frequency of adjudicated CAEs in the reslizumab versus placebo group, with similar results to the primary efficacy analysis. Thus, neither excluding the summed duration of CAEs, or any potential bias favouring reslizumab introduced by missing data, had a notable effect on the results of the primary efficacy analysis.

Table 31: Sensitivity analyses of the primary efficacy outcome

Sensitivity analysis	**Reslizumab 3.0 mg/kg N=232**	**Placebo N=232**
Analysis using offset variable that did not exclude summed duration of CAEs from follow-up time		
Adjusted CAE rate, mean (95% CI)	0.76 (0.50; 1.16)	1.73 (1.13; 2.66)
CAE rate ratio (95% CI), reslizumab vs placebo	0.44 (0.31; 0.62)	
p-value	<0.0001	
Analysis using multiple imputation method for missing data		
Adjusted CAE rate, mean (95% CI)	0.78 (0.55; 1.11)	1.97 (1.37; 2.84)
CAE rate ratio (95% CI), reslizumab vs placebo	0.40 (0.28; 0.57)	
p-value	<0.0001	

Sensitivity analysis	Reslizumab 3.0 mg/kg N=232	Placebo N=232
Analysis using both offset variable that did not exclude summed duration of CAEs from follow-up time and multiple imputation method for missing data		
Adjusted CAE rate, mean (95% CI)	0.69 (0.50; 0.95)	1.53 (1.10; 2.13)
CAE rate ratio (95% CI), reslizumab vs placebo	0.45 (0.30; 0.67)	
p-value	<0.0001	

Abbreviations: CAE, clinical asthma exacerbation; CI, confidence interval.

4.7.2.2 Secondary analysis of the primary outcome measure

Adjudicated CAEs by type of medical intervention

The analysis of CAE frequency by the type of medical intervention used to treat the event is presented in [redacted]. The most common intervention in both the reslizumab and placebo groups was treatment with a systemic corticosteroid (49/59 [83%] and 92/105 [88%] patients, respectively), most commonly administered orally (46/49 [94%] and 86/92 [93%] patients, respectively). The efficacy of reslizumab in reducing the frequency of CAEs in these two major patient subsets, versus placebo, was consistent with the results of the primary efficacy analysis.

Few patients required hospitalisation and/or an emergency room visit due to a CAE; the adjusted rate of these events was similar in the reslizumab and placebo groups.

[redacted]

[redacted]

[redacted] 4.7.2.8 [redacted].

Investigator-determined CAEs

The frequency of investigator-determined CAEs was analysed separately from CAEs identified by the adjudication committee. The results were similar to those obtained using the adjudicated data set; there was a significant reduction in CAE frequency with reslizumab compared with placebo (adjusted CAE rates were 1.11 and 2.42, respectively; rate ratio of 0.46 [95% CI: 0.33; 0.64]; nominal p<0.0001). The results of a sensitivity analysis using an offset variable that did not exclude the summed duration of CAEs from the follow-up time were consistent with the primary analysis of investigator-determined CAEs.

4.7.2.3 Secondary efficacy outcome: Change from baseline in FEV_1

A significantly greater improvement (increase) in FEV_1 was observed with reslizumab versus placebo for the change from baseline to Week 16 and the overall change over 16 weeks (Table 33). Although not controlled for multiple comparisons, treatment effects were also observed for the overall change over 52 weeks and at endpoint (nominal p-values were p=0.0057 and p=0.0016, respectively).

Table 33: Change from baseline in FEV_1 – randomised set

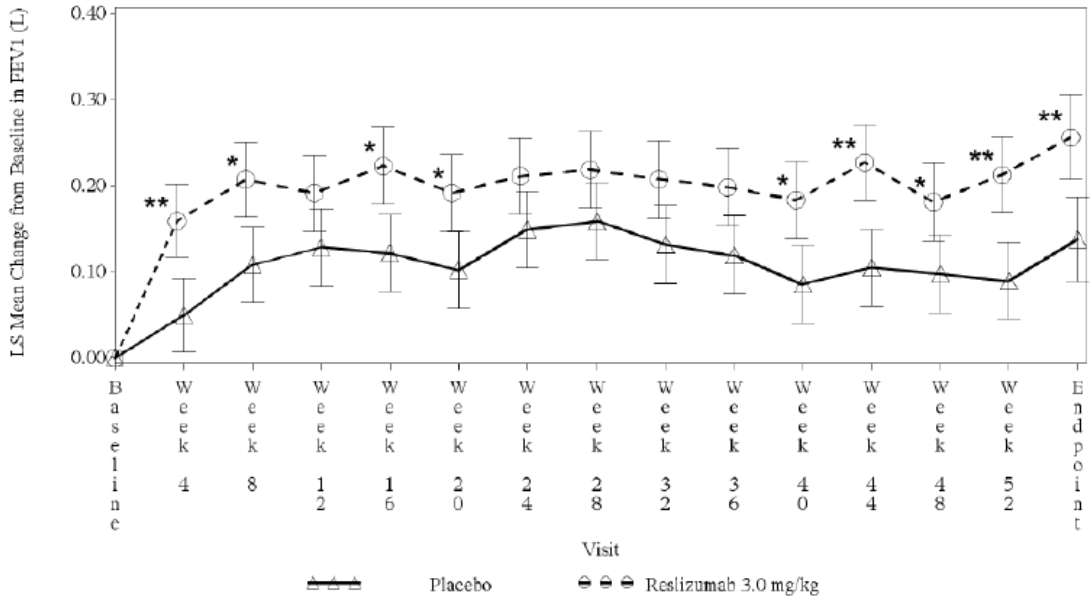
	Reslizumab 3.0 mg/kg N=232	**Placebo N=232**
Baseline FEV_1, L		
n	232	232
Mean (SD)	2.13 (0.78)	2.00 (0.67)

	Reslizumab 3.0 mg/kg N=232	Placebo N=232
Change in FEV_1 to Week 16, L		
n	214	214
Mean (SD)	0.25 (0.45)	0.15 (0.43)
LS mean (SE)	0.22 (0.04)	0.12 (0.04)
Treatment difference (SE), reslizumab – placebo	0.10 (0.04)	
95% CI	0.02; 0.18	
p-value	0.0109	
Change in FEV_1 over 16 weeks, L		
n	230	227
LS mean (SE)	0.19 (0.04)	0.09 (0.04)
Treatment difference (SE), reslizumab – placebo	0.09 (0.03)	
95% CI	0.03; 0.16	
p-value	0.0037	

Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in one second; L, litres; LS, least squares; SD, standard deviation; SE, standard error.

Change in FEV_1 from baseline to Weeks 4, 8, 12, 20, 24, 28, 32, 36, 40, 44, 48 and 52 (an 'other' efficacy outcome) is presented in Figure 13. A greater improvement in FEV_1 was observed with reslizumab versus placebo at the first assessment visit (Week 4) and at most subsequent visits.

Figure 13: Change from baseline in FEV_1 to each visit and endpoint – randomised set



Abbreviations: FEV_1, forced expiratory volume in one second; LS, least squares.
*Nominal p≤0.05 and **nominal p≤0.005; p-values were not adjusted to control for multiplicity. Data are LS means ± SE.

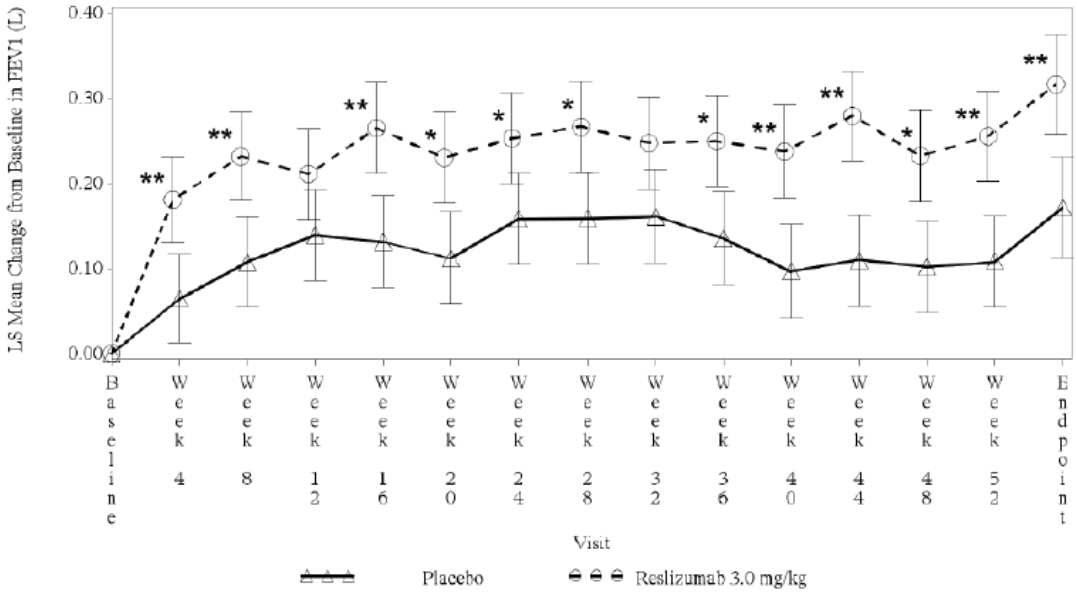
FEV_1 analysis set

The change from baseline in FEV_1 was also analysed in the more severe subpopulation of patients with a baseline % predicted FEV_1 value ≤85% (the FEV_1 analysis set; 180/232 [78%] and 185/232 [80%] patients in the reslizumab and placebo groups, respectively). LS mean change from baseline was:

- significantly greater with reslizumab versus placebo to Week 16 (0.27 L versus 0.13 L; treatment difference 0.13 [95% CI: 0.04; 0.22]; nominal p=0.0040)
- significantly greater with reslizumab versus placebo over 16 weeks (0.21 L versus 0.10 L; treatment difference 0.11 [95%CI: 0.04; 0.18]; nominal p=0.0033).

Similar to the analysis using the randomised set, a greater improvement in FEV_1 was observed with reslizumab versus placebo at Week 4 and throughout the study in the FEV_1 analysis set (Figure 14).

Figure 14: Change from baseline in FEV_1 to each visit and endpoint – FEV_1 analysis set



Abbreviations: FEV_1, forced expiratory volume in one second.
**Nominal p≤0.005; p-values were not adjusted to control for multiplicity. Data are LS means ± SE.

4.7.2.4 Secondary efficacy outcome: Change from baseline in AQLQ score

There was a significantly greater improvement (increase) in AQLQ total score from baseline to Week 16 in the reslizumab group compared with the placebo group (Table 34. Although not controlled for multiplicity of testing, greater improvements in AQLQ score were also seen with reslizumab versus placebo over 52 weeks and at endpoint (nominal p=0.0052 and nominal p=0.0043, respectively).

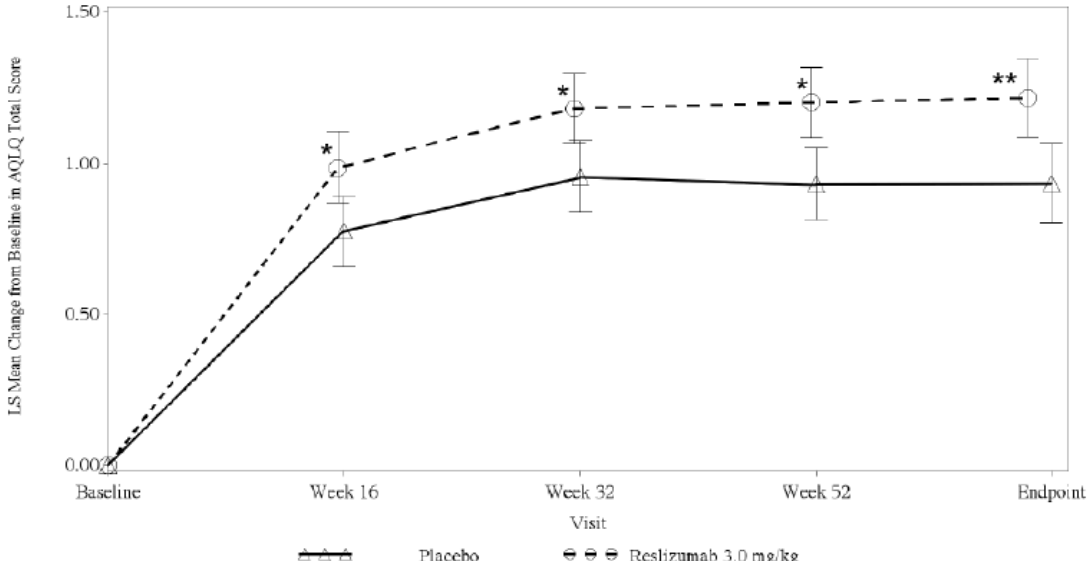
Table 34: Change from baseline in AQLQ total score – randomised set

	Reslizumab 3.0 mg/kg N=232	Placebo N=232
Baseline AQLQ total score		
n	229	231
Mean (SD)	4.35 (1.02)	4.22 (1.08)
Change in AQLQ total score to Week 16		
n	213	216
Mean (SD)	0.95 (1.10)	0.79 (1.14)
LS mean (SE)	0.99 (0.12)	0.78 (0.12)
Treatment difference (SE), reslizumab – placebo	0.21 (0.09)	
95% CI	0.03; 0.39	
p-value	0.0259	

Abbreviations: AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; LS, least squares; SD, standard deviation; SE, standard error.

Change in AQLQ total score from baseline to Weeks 32 and 52 was analysed as an 'other' efficacy outcome. The greater improvement observed with reslizumab at Week 16 was sustained at both timepoints (Figure 15). Treatment differences were also observed for the change from baseline to Weeks 16 and 52 in each of the four AQLQ score domains (not shown).

Figure 15: Change from baseline in AQLQ total score to each visit and endpoint – randomised set



Abbreviations: AQLQ, Asthma Quality of Life Questionnaire. *Nominal p≤0.05 and **nominal p≤0.005; p-values were not adjusted to control for multiplicity. Data are LS means ± SE.

AQLQ responders

The proportion of patients achieving at least a 0.5-point improvement in AQLQ total score was [redacted] with reslizumab versus placebo at Week 16 ([redacted]% vs [redacted]%; nominal p=[redacted]) and Week 52 ([redacted]% vs [redacted]%; nominal p=[redacted]); a numerically greater improvement was observed at Week 32 ([redacted]% vs [redacted]%; nominal p=[redacted]) (***[redacted]16). A [redacted] of responders was also observed with reslizumab versus placebo for each of the four AQLQ domain scores at Weeks 16, 32, and 52 and at endpoint (not shown).

[redacted]16

Abbreviations: AQLQ, Asthma Quality of Life Questionnaire; U, unit.
*Nominal p≤0.05; p-value was not adjusted to control for multiplicity.

4.7.2.5 Secondary efficacy outcome: Change from baseline in ACQ score

Analysis of the overall change in ACQ total score over 16 weeks demonstrated a significantly greater improvement (decrease) for patients treated with reslizumab versus placebo (Table 35). Although not controlled for multiplicity of testing, a treatment effect was also seen from baseline to Week 16, over 52 weeks and at endpoint (nominal p-values were 0.0121, 0.0003 and 0.0001, respectively.

Change from baseline in ACQ total score from baseline to each treatment visit is presented in Figure 17 (analysed as an 'other' efficacy outcome); a greater improvement was observed with reslizumab versus placebo at the first 4-week assessment visit and throughout the study.

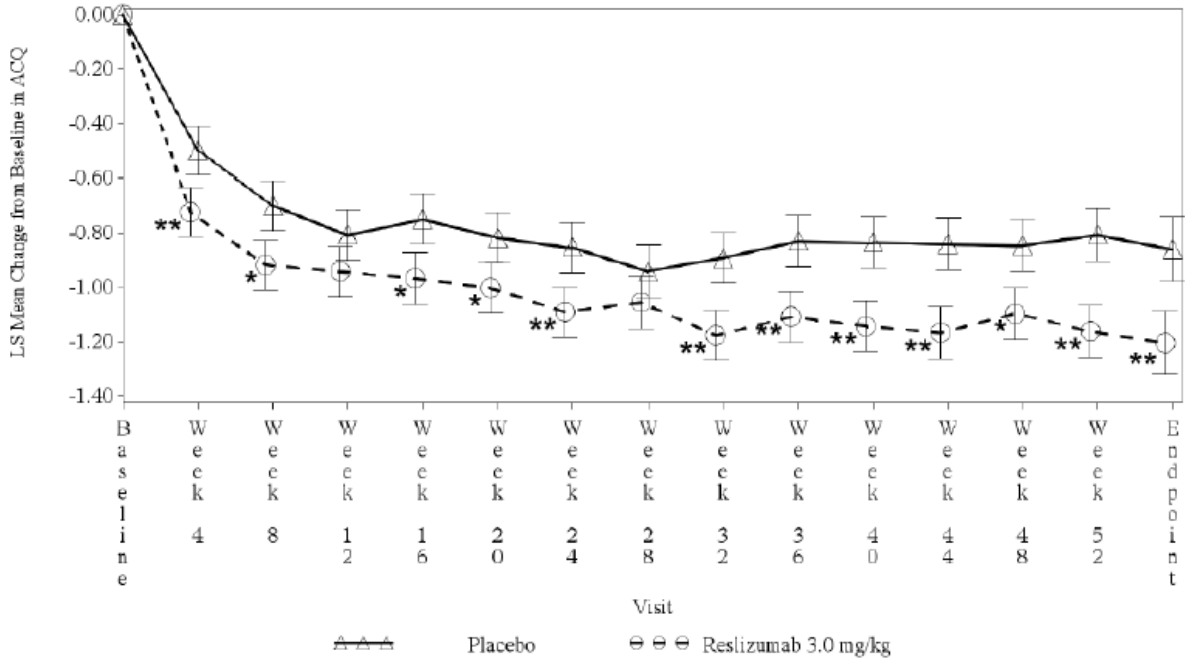
Table 35: Change from baseline in ACQ total score – randomised set

	Reslizumab 3.0 mg/kg N=232	**Placebo N=232**

	Reslizumab 3.0 mg/kg N=232	Placebo N=232
Baseline ACQ total score		
n	232	232
Mean (SD)	2.57 (0.89)	2.61 (0.79)
Change in ACQ total score over 16 weeks		
n	230	228
LS mean (SE)	–0.86 (0.09)	–0.66 (0.09)
Treatment difference (SE), reslizumab – placebo	–0.20 (0.07)	
95% CI	–0.33; –0.07	
p-value	0.0032	

Abbreviations: ACQ, Asthma Control Questionnaire; CI, confidence interval; LS, least squares; SD, standard deviation; SE, standard error.

Figure 17: Change from baseline in ACQ total score to each visit and endpoint – randomised set



Abbreviations: ACQ, Asthma Control Questionnaire; LS, least squares; U, unit.
*Nominal p≤0.05 and **nominal p≤0.005; p-values were not adjusted to control for multiplicity.

ACQ responders

The proportion of patients achieving at least a 0.5-point improvement in ACQ total score was [redacted] with reslizumab versus placebo at each treatment visit except for Week 12 (***[redacted]18). The proportion of responders was [redacted]% and [redacted]%, respectively, at Week 16 (nominal p=[redacted]), and [redacted]% and [redacted]%, respectively, at Week 52 (nominal [redacted]).

Abbreviations: ACQ, Asthma Control Questionnaire; U, unit.
*Nominal p≤0.05 and **nominal p≤0.005; p-values were not adjusted to control for multiplicity.

4.7.2.6 Secondary efficacy outcome: Time to first CAE

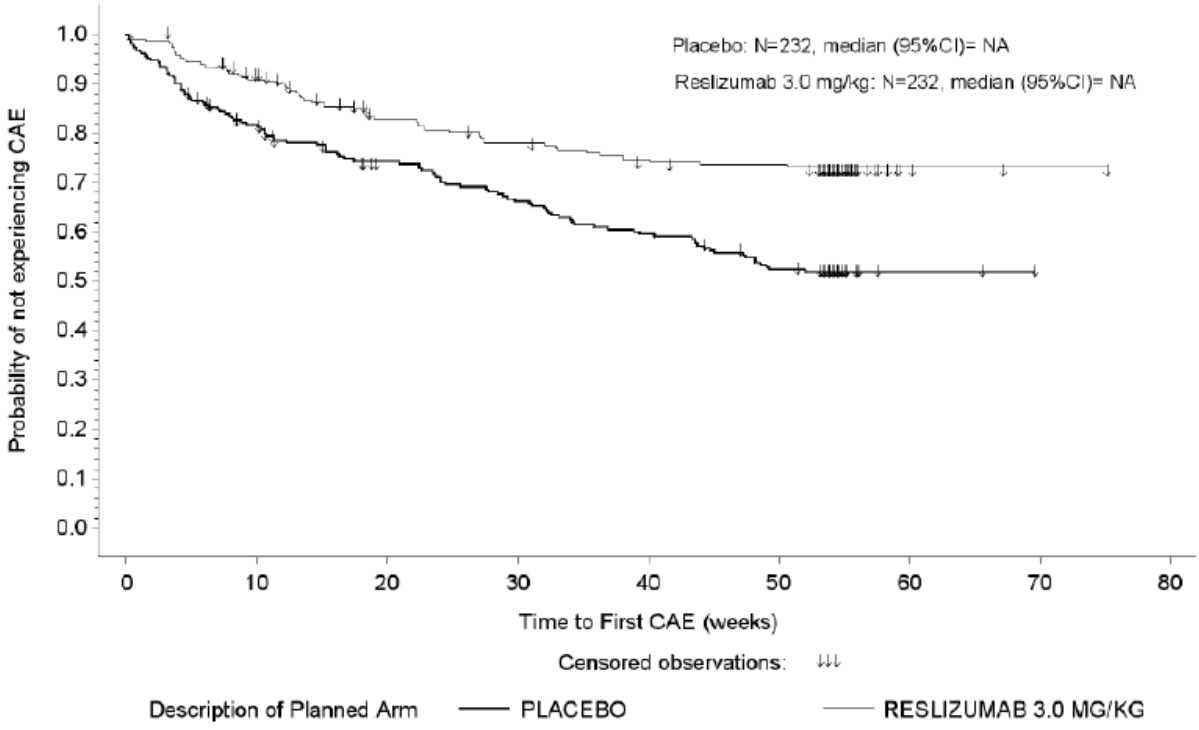
The probability of not experiencing a CAE by Week 52 was found to be significantly greater in the reslizumab group versus placebo (Table 36 and Figure 19). The median time to first CAE could not be estimated for either treatment group because <50% of patients in each group experienced at least one CAE (see Table 30).

Table 36: Time to first CAE – randomised set (adjudicated data)

	Reslizumab 3.0 mg/kg N=232	**Placebo N=232**
Kaplan-Meier estimate		
Quartile 1, weeks (95% CI)	38.0 (24.7; NA)	16.7 (10.6; 25.6)
Median, weeks (95% CI)	NA	NA
Quartile 3, weeks (95% CI)	NA	NA
Kaplan-Meier estimate of probability of not experiencing a CAE by Week 52		
% (95% CI)	73.2 (66.8; 78.6)	51.9 (45.0; 58.3)
Hazard ratio (95% CI), reslizumab vs placebo	0.49 (0.35; 0.67)	
p-value	<0.0001	

Abbreviations: CAE, clinical asthma exacerbation; CI, confidence interval; NA, not applicable.

Figure 19: Time to first CAE – randomised set (adjudicated data)



Abbreviations: CAE, clinical asthma exacerbation; CI, confidence interval; NA, not applicable.

Patients with CAEs requiring systemic corticosteroids

Time to first CAE was also analysed for the subgroup of patients who experienced a CAE that required treatment with systemic (primarily oral) corticosteroids. Similar results were observed for this subgroup as with all patients who experienced a CAE. The Kaplan-Meier estimate of probability of not experiencing a CAE requiring systemic corticosteroids by Week 52 was 77.7% (95% CI: 71.6; 82.7) with reslizumab and 57.9% (95% CI: 51.0; 64.1) with placebo (hazard ratio [reslizumab vs placebo] of 0.47 [95% CI: 0.33; 0.67], nominal p<0.0001).

4.7.2.7 Secondary efficacy outcome: Change from baseline in ASUI score

A significantly greater improvement (increase) in ASUI total score over 16 weeks was observed in the reslizumab group compared with the placebo group (Table 37). A treatment effect was also observed for the change from baseline to Week 16 (nominal p=0.0235), over 52 weeks (nominal p=0.0011) and at endpoint (nominal p=0.0057).

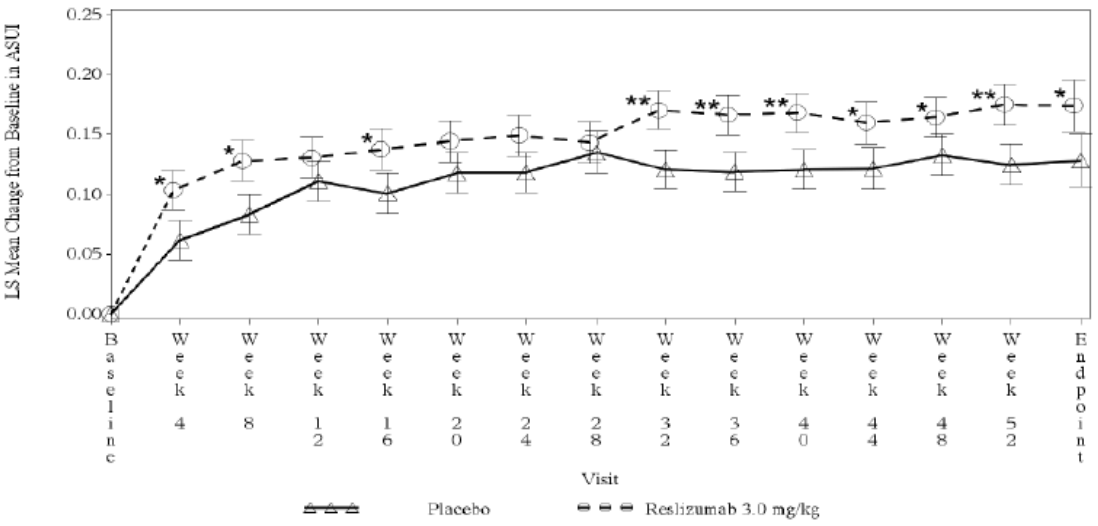
Change from baseline in ASUI total score to each treatment visit was analysed as an 'other' efficacy outcome; a greater improvement was observed in the reslizumab group than the placebo group at Week 4 and at most subsequent visits throughout the study (Figure 20).

Table 37: Change from baseline in ASUI score – randomised set

	Reslizumab 3.0 mg/kg N=232	Placebo N=232
Baseline ASUI total score		
n	228	229
Mean (SD)	0.66 (0.20)	0.65 (0.19)
Change in ASUI total score over 16 weeks		
n	227	224
LS mean (SE)	0.12 (0.02)	0.08 (0.02)
Treatment difference (SE), reslizumab – placebo	0.04 (0.01)	
95% CI	0.01; 0.06	
p-value	0.0037	

Abbreviations: ASUI, Asthma Symptom Utility Index; CI, confidence interval; LS, least squares; SD, standard deviation; SE, standard error.

Figure 20: Change from baseline in ASUI score to each visit and endpoint – randomised set



Abbreviations: ASUI, Asthma Symptom Utility Index; LS, least squares.
*Nominal p≤0.05 and **nominal p≤0.005; p-values were not adjusted to control for multiplicity.

4.7.2.8 Secondary efficacy outcome: Change from baseline in SABA use

There was a numerically greater improvement (decrease in daily use) in the change in SABA use over 16 weeks with reslizumab compared with placebo, but the difference was small and not statistically significant (Table 38). Treatment differences at Week 16, over 52 weeks and at endpoint were also small and not significant.

Change from baseline in daily SABA use to each treatment visit was analysed as an 'other' efficacy outcome. Although there was a general trend for a greater reduction in use with reslizumab versus placebo, the difference was not significant at any of the scheduled visits.

Table 38: Change from baseline in SABA use – randomised set

	Reslizumab 3.0 mg/kg N=232	Placebo N=232
Patients using SABA at baseline		
n	226	227
Yes, n (%)	182 (81)	181 (80)
Average SABA use at baseline		
n	204	201
Puffs/day, mean (SD)	2.9 (2.82)	2.7 (2.41)
Change in SABA use (puffs/day) over 16 weeks		
n	180	188
LS mean (SE)	–0.50 (0.23)	–0.44 (0.23)
Treatment difference (SE), reslizumab – placebo	–0.06 (0.18)	
95% CI	–0.41; 0.29	
p-value	0.7263	

Abbreviations: CI, confidence interval; LS, least squares; SABA, short-acting beta-agonist; SD, standard deviation; SE, standard error.

4.7.2.9 Secondary efficacy outcome: Change from baseline in blood eosinophil count

There was a significantly greater decrease in blood eosinophil count over 16 weeks and 52 weeks in the reslizumab group compared with the placebo group (Table 39). Significant treatment differences were also observed for the change from baseline to Week 16 and at endpoint (nominal p<0.0001 for both).

Table 39: Change from baseline in blood eosinophil count – randomised set

	Reslizumab 3.0 mg/kg N=232	Placebo N=232
Baseline blood eosinophil count, cells/µL[†]		
n	232	232
Mean (SD)	610 (411.5)	688 (682.4)
Overall change in blood eosinophil count over 16 weeks[‡], cells/µL		
n	230	226
LS mean (SE)	–555 (26.6)	–76 (26.8)
Treatment difference (SE), reslizumab – placebo	–479 (20.3)	
95% CI	–519; –439	
p-value	<0.0001	

	Reslizumab 3.0 mg/kg N=232	Placebo N=232
Overall change in blood eosinophil count over 52 weeks[‡], cells/µL		
n	230	226
LS mean (SE)	–565 (23.1)	–76 (23.3)
Treatment difference (SE), reslizumab – placebo	–489 (18.4)	
95% CI	–525; –453	
p-value	<0.0001	

Abbreviations: CI, confidence interval; LS, least squares; SD, standard deviation; SE, standard error.
[†]Patients were required to have a blood eosinophil count ≥400/µL at least once during the screening period; however, as this value did not necessarily occur at baseline, baseline eosinophil counts for the randomised set include some patients with values <400/µL.
[‡]Because the results of the preceding secondary efficacy analysis (SABA use over 16 weeks) were not statistically significant, the analysis of change from baseline in blood eosinophil count over 16 and 52 weeks was not controlled for multiplicity.

Blood eosinophil count at each treatment visit was analysed as an 'other' efficacy outcome ([redacted]21); a greater reduction was observed with reslizumab versus placebo at the first assessment visit and was sustained throughout the study.

At the 90-day follow-up visit, blood eosinophil counts were available for only [redacted] patients in the reslizumab group and [redacted] patients in the placebo group, as most patients enrolled in the open-label extension study C38072/3085. However, in this small cohort there was evidence of a [redacted] in blood eosinophil count (cells/µL) back towards a baseline level in the reslizumab group (from a mean±SD of [redacted]±[redacted] at Week 52 to [redacted]±[redacted] at follow-up); the follow-up count was still lower than that in the placebo group at follow-up ([redacted]±[redacted]).

[redacted]21

Horizontal bars indicate mean values.

4.7.2.10 Other efficacy outcomes

The analyses of change from baseline to specific visits in FEV_1, ASUI total score, ACQ total score, AQLQ total score, SABA use and blood eosinophil count are presented in Section 4.7.2.3 to Section 4.7.2.9 with the results of the relevant secondary efficacy variables. For the remaining analyses of lung function, no adjustments for multiplicity were applied and thus p-values are nominal. Significantly greater improvements with reslizumab versus placebo were observed for the outcomes listed below.

- **Change from baseline in FVC:**
  - over 16 weeks (treatment difference 0.08 L [95% CI: 0.01; 0.15], p=0.0326)
  - over 52 weeks (treatment difference 0.08 L [95% CI: 0.01; 0.16], p=0.0202)
  - at endpoint (treatment difference 0.11 L [95% CI: 0.03; 0.20], p=0.0099).
- **Change from baseline in % predicted FEV_1:**
  - to Week 16 (treatment difference 3.20 L [95% CI: 0.66; 5.74], p=0.0136)
  - over 16 weeks (treatment difference 3.05 L [95% CI: 1.01; 5.10], p=0.0035)
  - over 52 weeks (treatment difference 3.18 L [95% CI: 1.12; 5.23], p=0.0025)
  - at endpoint (treatment difference 3.89 L [95% CI: 1.54; 6.24], p=0.0012).

$FEF_{25–75\%}$ was also [redacted] with reslizumab vs placebo from baseline to Week 16 (p=[redacted]), over 16 weeks (p=[redacted]), over 52 weeks (p=[redacted]), and at endpoint (p=[redacted]). However, these [redacted]

4.7.2.11 Exploratory variables

Analyses of exploratory variables were not adjusted for multiplicity and thus p-values are nominal.

Sputum eosinophil count

Sputum samples were analysed for only [redacted] patients at baseline ([redacted] reslizumab and [redacted] placebo), precluding meaningful interpretation of any changes from baseline.

Change from baseline in PEFR

PEFR data were available for only [redacted]% of randomised patients in each group at baseline and approximately [redacted]% of patients at Week 52. There was a [redacted] in PEFR with reslizumab versus placebo for the outcomes listed below.

- **Change from baseline in weekly average of daily morning PEFR:**
  - over 16 weeks (treatment difference [redacted] L [95% CI: 5.7; 37.2], p=[redacted])
  - over 52 weeks (treatment difference [redacted] L [95% CI: 4.4; 36.3], p=[redacted])
  - to Week 16 (treatment difference [redacted] L [95% CI: 7.4; 43.1], p=[redacted])
  - to endpoint (treatment difference [redacted] L [95% CI: 1.5; 36.4], p=[redacted]).
- **Change from baseline in weekly average of daily evening PEFR**
  - over 16 weeks (treatment difference [redacted] L [95% CI: 10.1; 42.3], p=[redacted])
  - over 52 weeks (treatment difference [redacted] L [95% CI: 6.6; 39.6], p=[redacted])
  - to Week 16 (treatment difference [redacted] L [95% CI: 9.9; 46.8], p=[redacted])
  - to endpoint (treatment difference [redacted] L [95% CI: 10.3; 47.0], p=[redacted]).

4.7.2.12 Efficacy conclusions

The primary efficacy results from C38072/3083 show that reslizumab 3.0 mg/kg, administered intravenously every 4 weeks over 52 weeks, is effective in controlling asthma exacerbations in patients with asthma and elevated blood eosinophils (≥400/µL) inadequately controlled by medium to high dose ICS.

Reslizumab treatment also improves lung function (FEV_1), asthma control (ACQ score), asthma symptoms (ASUI score) and asthma QoL (AQLQ score), and leads to a reduction in blood eosinophils consistent with the mechanism of action of this IL-5 monoclonal antibody.

4.7.3 *C38072/3081*

4.7.3.1 Primary efficacy outcome: Change from baseline in FEV_1 over 16 weeks

There was a significantly greater improvement (increase) in FEV_1 over 16 weeks in both reslizumab groups compared with placebo. The overall treatment effect was larger for patients in the reslizumab 3.0 mg/kg group than in the 0.3 mg/kg group (Table 40).

Change in FEV_1 from baseline to other timepoints (Weeks 4, 8, 12, and 16 and endpoint) was analysed as a secondary outcome (Table 40 and Figure 22). A treatment effect was seen with reslizumab 3.0 mg/kg at the first 4-week assessment (0.15 L, p=0.003) and was sustained at Week 16 (0.17 L, p=0.0118). Improvements in the reslizumab 0.3 mg/kg group were more variable, but were numerically or significantly greater than those in the placebo group at each visit.

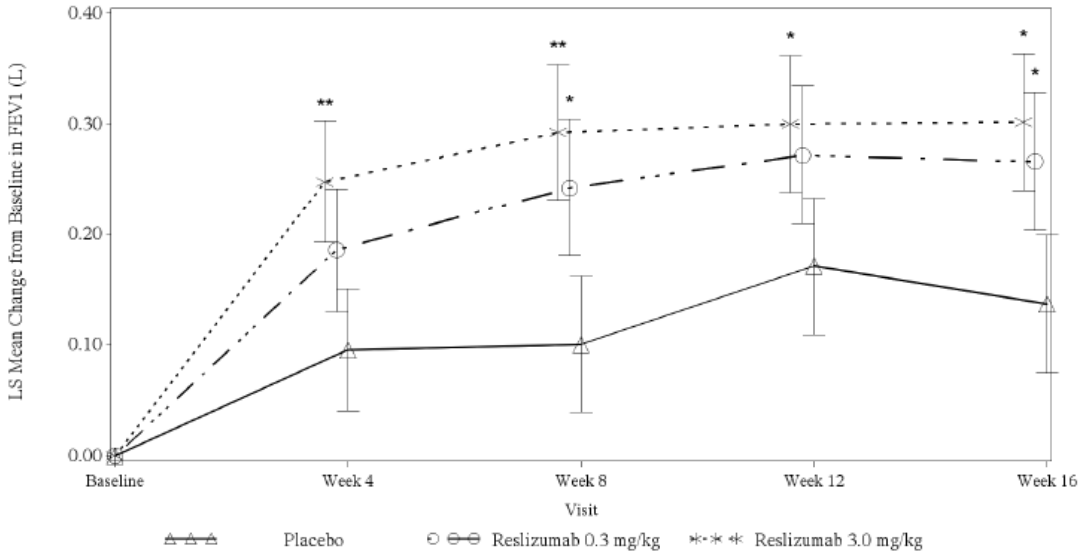
Table 40: Change from baseline in FEV_1 – full analysis set

	Reslizumab 0.3 mg/kg N=103	**Reslizumab 3.0 mg/kg N=103**	**Placebo N=105**
Baseline FEV_1, L			
n	103	103	105
Mean (SD)	2.16 (0.85)	2.17 (0.78)	2.22 (0.81)
Change in FEV_1 over 16 weeks, L			
n	101	102	103
LS mean (SE)	0.24 (0.06)	0.29 (0.05)	0.13 (0.05)
Treatment difference (SE), reslizumab – placebo	0.12 (0.05)	0.16 (0.05)	NA
95% CI	0.02; 0.22	0.06; 0.26	NA
p-value	0.0237	0.0018	NA

	Reslizumab 0.3 mg/kg N=103	Reslizumab 3.0 mg/kg N=103	Placebo N=105
Change in FEV_1 at Week 16†, L			
n	92	91	84
Mean (SD)	0.19 (0.56)	0.24 (0.48)	0.05 (0.39)
LS mean (SE)	0.27 (0.06)	0.30 (0.06)	0.14 (0.06)
Treatment difference (SE), reslizumab – placebo	0.13 (0.07)	0.17 (0.07)	NA
95% CI	0.001; 0.26	0.04; 0.29	NA
p-value	0.0481	0.0118	NA
Change in FEV_1 at endpoint†, L			
n	101	102	103
Mean (SD)	0.20 (0.55)	0.22 (0.48)	0.05 (0.42)

Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in one second; L, litres; LS, least squares; NA, not applicable; SD, standard deviation; SE, standard error.
†Change in FEV1 from baseline to Week 16 and to endpoint was analysed as a secondary outcome.

Figure 22: Change from baseline in FEV_1 by visit – full analysis set



Abbreviations: FEV_1, forced expiratory volume in one second; LS, least squares.
*Nominal p≤0.05 and **nominal p≤0.005; p-values were not adjusted to control for multiplicity. Data are LS means ± SE.

Sensitivity analyses of the primary outcome

The results of sensitivity analyses using 1) all FEV_1 measurements without data exclusions for confounding medications (see Section 4.4.1.2) and 2) multiple imputation for missing data are presented in Table 41 and

Table 42, respectively. Both sensitivity analyses demonstrated a significantly greater improvement in FEV_1 with reslizumab versus placebo over 16 weeks, with similar results to the primary analysis.

Table 41: Sensitivity analysis of the primary efficacy outcome – analysis using all FEV_1 measurements without data exclusions for confounding medications – full analysis set

	Reslizumab 0.3 mg/kg N=103	Reslizumab 3.0 mg/kg N=103	Placebo N=105
Baseline FEV_1, L			
n	103	103	105
Mean (SD)	2.16 (0.85)	2.17 (0.78)	2.22 (0.81)
Change in FEV_1 over 16 weeks, L			
n	101	102	103
LS mean (SE)	0.24 (0.06)	0.29 (0.05)	0.13 (0.05)
Treatment difference (SE), reslizumab – placebo	0.11 (0.05)	0.16 (0.05)	NA
95% CI	0.01; 0.21	0.06; 0.26	NA
p-value	0.0283	0.0018	NA
Change in FEV_1 at Week 16†, L			
n	92	91	84
Mean (SD)	0.19 (0.56)	0.24 (0.48)	0.05 (0.39)
LS mean (SE)	0.26 (0.06)	0.30 (0.06)	0.14 (0.06)
Treatment difference (SE), reslizumab – placebo	0.13 (0.06)	0.17 (0.07)	NA
95% CI	–0.003, 0.253	0.037, 0.292	NA
p-value	0.0555	0.0118	NA
Change in FEV_1 at endpoint†, L			
n	101	102	103
Mean (SD)	0.19 (0.54)	0.22 (0.48)	0.05 (0.42)

Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in one second; L, litres; LS, least squares; NA, not applicable; SD, standard deviation; SE, standard error.
†Post hoc sensitivity analysis of secondary efficacy outcome.

Table 42: Sensitivity analysis of the primary efficacy outcome – analysis using multiple imputation method for missing data – full analysis set

	Reslizumab 0.3 mg/kg N=103	Reslizumab 3.0 mg/kg N=103	Placebo N=105
Change in FEV_1 over 16 weeks, L			
n	103	103	105
LS mean (SE)	0.26 (0.06)	0.29 (0.06)	0.09 (0.06)
Treatment difference (SE), reslizumab – placebo	0.17 (0.05)	0.21 (0.05)	NA
95% CI	0.07; 0.28	0.10; 0.31	NA
p-value	0.0012	0.0001	NA

Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in one second; L, litres; LS, least squares; NA, not applicable; SE, standard error.

4.7.3.2 Secondary analysis of the primary outcome measure: Change from baseline in FEV_1 over 16 weeks for the FEV_1 analysis set

The change from baseline in FEV_1 was also analysed in the FEV_1 analysis set. In this more severe subgroup, an improvement in FEV_1 was observed in both reslizumab groups versus placebo; however only the result for the 3.0 mg/kg group was statistically significant (Table 43). Of note, this analysis was performed on a smaller population, for which the study was not powered.

Table 43: Change from baseline in FEV_1 – FEV_1 analysis set

	Reslizumab 0.3 mg/kg N=103	Reslizumab 3.0 mg/kg N=103	Placebo N=81
Change in FEV_1 over 16 weeks, L			
n	84	81	79
LS mean (SE)	0.29 (0.07)	0.36 (0.07)	0.20 (0.07)
Treatment difference (SE), reslizumab – placebo	0.09 (0.06)	0.17 (0.06)	NA
95% CI	–0.03, 0.20	0.05, 0.28	NA
p-value	0.1479	0.0066	NA

Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in one second; L, litres; LS, least squares; NA, not applicable; SE, standard error.

4.7.3.3 Secondary efficacy outcome: Change from baseline in FEV_1 to Weeks 4, 8, 12, and 16 and endpoint

The secondary analysis of change from baseline in FEV_1 is presented in Section 4.7.3.1 with the results of the primary analysis.

4.7.3.4 Secondary efficacy outcome: Change from baseline in FVC

A significantly greater improvement (increase) in FVC over 16 weeks was observed with reslizumab 3.0 mg/kg compared with placebo. The treatment effect for the reslizumab 0.3 mg/kg group was not significant (Table 44). A significant improvement was observed for patients in the reslizumab 3.0 mg/kg group at Week 8 (0.153 L, p=0.0190) and was sustained throughout the 16-week treatment period. Improvements for patients in the 0.3 mg/kg group were numerically, but not significantly, greater than placebo at each clinic visit (Figure 23).

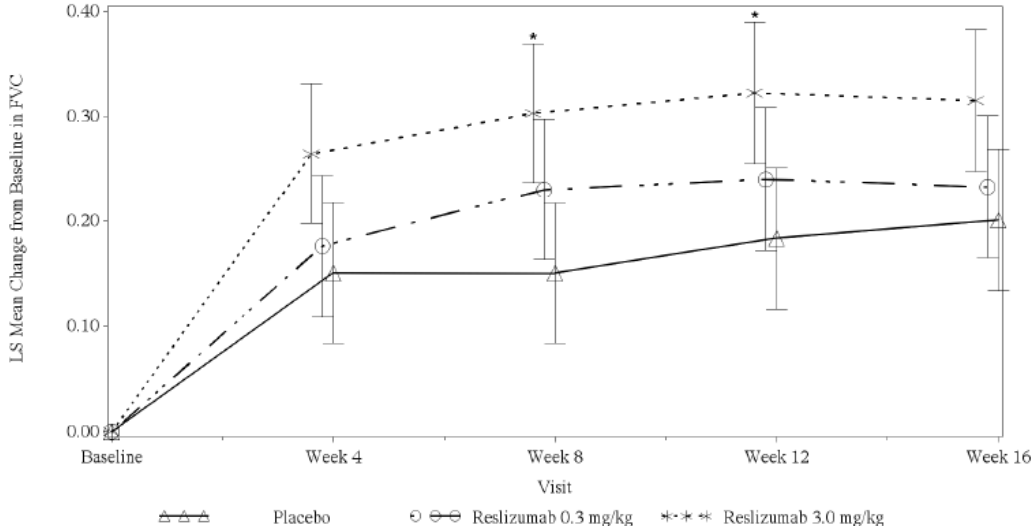
The results of a post hoc sensitivity analysis using all measurements without data exclusions for confounding medications were consistent with those based on the FAS.

Table 44: Change from baseline in FVC – full analysis set

	Reslizumab 0.3 mg/kg N=103	**Reslizumab 3.0 mg/kg N=103**	**Placebo N=105**
Baseline FVC, L			
n	103	103	105
Mean (SD)	3.29 (1.12)	3.20 (1.01)	3.29 (1.05)
Change in FVC over 16 weeks, L			
n	101	102	103
LS mean (SE)	0.22 (0.06)	0.30 (0.06)	0.17 (0.06)
Treatment difference (SE), reslizumab – placebo	0.05 (0.05)	0.13 (0.05)	NA
95% CI	–0.06; 0.16	0.02; 0.24	NA
p-value	0.3731	0.0174	NA
Change in FVC at Week 16, L			
n	92	90	84
LS mean (SE)	0.23 (0.07)	0.32 (0.07)	0.20 (0.07)
Treatment difference (SE), reslizumab – placebo	0.03 (0.07)	0.11 (0.07)	NA
95% CI	–1.10; 0.17	–0.02; 0.25	NA
p-value	0.6382	0.0930	NA
Change in FVC at endpoint, L			
n	101	102	103
Mean (SD)	0.15 (0.49)	0.23 (0.52)	0.09 (0.49)

Abbreviations: CI, confidence interval; FVC, forced vital capacity; L, litres; LS, least squares; NA, not applicable; SD, standard deviation; SE, standard error.

Figure 23: Change from baseline in FVC – full analysis set



Abbreviations: FVC, forced vital capacity.
*Nominal p≤0.05; p-values were not adjusted to control for multiplicity. Data are LS means ± SE.

4.7.3.5 Secondary efficacy outcome: Change from baseline in $FEF_{25–75\%}$

$FEF_{25\%-75\%}$ over 16 weeks of treatment was [redacted] with reslizumab 3.0 mg/kg compared with placebo (p=[redacted]); the treatment effect for patients treated with reslizumab 0.3 mg/kg was [redacted] and also [redacted] (p=[redacted]; [redacted]45). Analyses by visit demonstrated a [redacted] for reslizumab 3.0 mg/kg versus placebo at Week 4 only ([redacted]24).

The results of a post hoc sensitivity analysis using all measurements without data exclusions for confounding medications were consistent with those based on the FAS.

[redacted]45

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

[redacted]

[redacted]

Abbreviations: $FEF_{25–75\%}$, forced expiratory flow at 25–75% forced vital capacity. Data are LS means ± SE.

4.7.3.6 Secondary efficacy outcome: Change from baseline in % predicted FEV_1

Change from baseline in % predicted FEV_1 was summarised descriptively. Patients in both reslizumab groups had a greater mean increase in % predicted FEV_1 at Week 16 compared with placebo (Table 46). Improvements were seen with reslizumab at the first 4-week assessment visit and were sustained throughout the study (Figure 25).

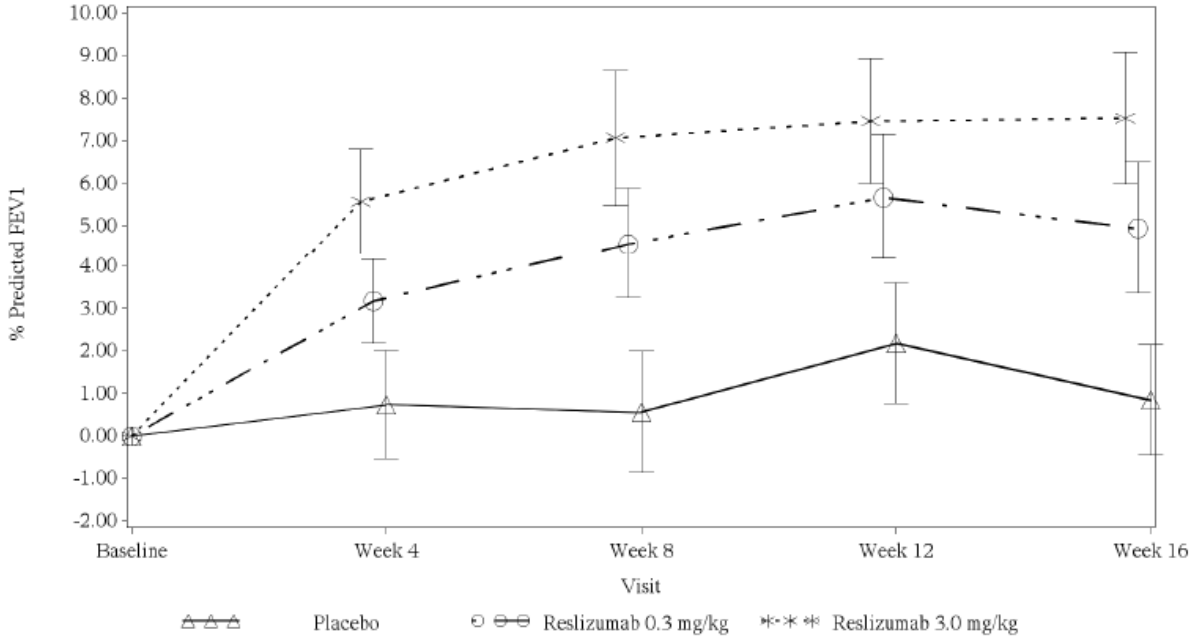
Change from baseline in % predicted FEV_1 was also summarised post hoc using all measurements without data exclusions for confounding medications. The results of this sensitivity analysis were consistent with those based on the FAS.

Table 46: Change from baseline in % predicted FEV_1 – full analysis set

	Reslizumab 0.3 mg/kg N=103	Reslizumab 3.0 mg/kg N=103	Placebo N=105
Baseline % predicted FEV_1, L			
n	103	103	105
Mean (SD)	68.8 (18.48)	70.0 (18.31)	71.1 (19.84)
Change in % predicted FEV_1 at Week 16, L			
n	92	91	84
Mean (SD)	4.9 (15.06)	7.5 (14.74)	0.8 (11.92)
Change in % predicted FEV_1 at endpoint, L			
n	101	102	103
Mean (SD)	5.5 (15.16)	6.7 (15.01)	0.8 (13.83)

Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in one second; L, litres; SD, standard deviation.

Figure 25: Change from baseline in % predicted FEV_1 – full analysis set



Abbreviations: FEV_1, forced expiratory volume in one second. Data are LS means ± SE.

4.7.3.7 Secondary efficacy outcome: Change from baseline in ACQ score

There was a significantly greater improvement (decrease) in ACQ over 16 weeks in the reslizumab 0.3 mg/kg and 3.0 mg/kg groups compared with placebo (Table 47). An improvement was observed with reslizumab 3.0 mg/kg at the first assessment visit and throughout the study; improvements for patients in the 0.3 mg/kg group were more variable, but were at least numerically greater versus placebo at each visit (Figure 26).

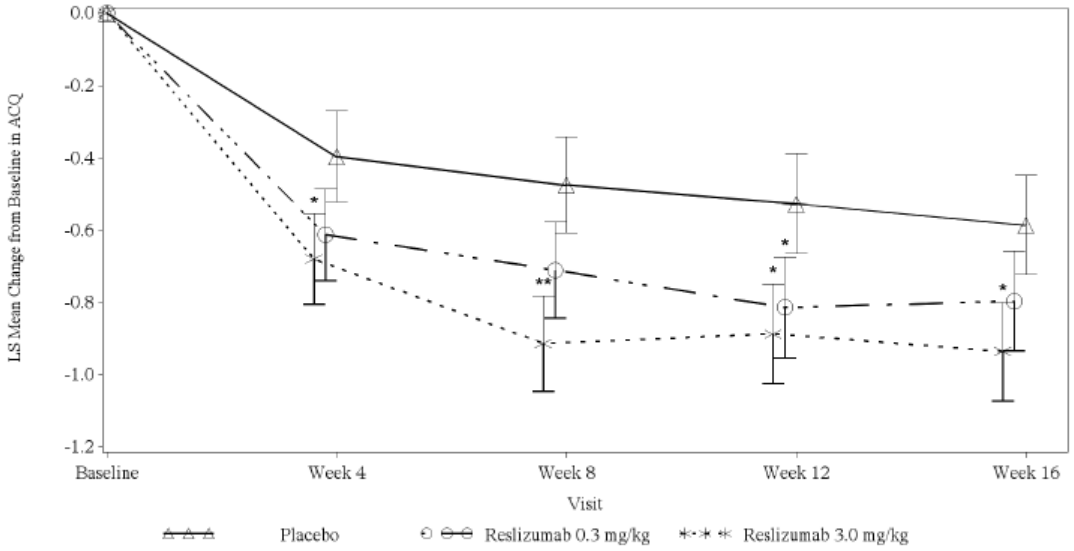
A post hoc sensitivity analysis was performed using all measurements without data exclusions for confounding medications; the results were consistent with those based on the FAS.

Table 47: Change from baseline in ACQ total score – full analysis set

	Reslizumab 0.3 mg/kg N=103	**Reslizumab 3.0 mg/kg N=103**	**Placebo N=105**
Baseline ACQ score			
n	103	103	105
Mean (SD)	2.50 (0.89)	2.59 (0.89)	2.47 (0.83)
Change in ACQ score over 16 weeks			
n	101	101	103
LS mean (SE)	–0.73 (0.13)	–0.85 (0.12)	–0.49 (0.12)
Treatment difference (SE), reslizumab – placebo	–0.24 (0.11)	–0.36 (0.11)	NA
95% CI	–0.46; –0.02	–0.58; –0.14	NA
p-value	0.0329	0.0014	NA
Change in ACQ score at Week 16			
n	92	91	84
LS mean (SE)	–0.80 (0.14)	–0.94 (0.14)	–0.58 (0.14)
Treatment difference (SE), reslizumab – placebo	–0.21 (0.14)	–0.35 (0.14)	NA
95% CI	–0.49; 0.06	–0.63; 0.08	NA
p-value	0.1327	0.0129	NA
Change in ACQ score at endpoint			
n	101	101	103
Mean (SD)	–0.80 (0.99)	–0.99 (1.19)	–0.53 (1.02)

Abbreviations: CI, confidence interval; ACQ, Asthma Control Questionnaire; L, litres; LS, least squares; NA, not applicable; SD, standard deviation; SE, standard error.

Figure 26: Change from baseline in ACQ total score – full analysis set



Abbreviations: ACQ, Asthma Control Questionnaire.
*Nominal p≤0.05 and **nominal p≤0.005; p-values were not adjusted to control for multiplicity. Data are LS means ± SE.

ACQ responders

The proportion of patients achieving at least a 0.5-point improvement in ACQ score was [redacted] with both reslizumab 0.3 mg/kg ([redacted]%) and reslizumab 3.0 mg/kg ([redacted]%) versus placebo ([redacted]%) at Week 4 (p=[redacted] and p=[redacted], respectively). The proportion of responders remained [redacted] for patients treated with either dose of reslizumab versus placebo at each subsequent visit; however, the between-group differences [redacted], possibly due in part to a [redacted] ([redacted]27).

[redacted]27[redacted]

Abbreviations: ACQ, Asthma Control Questionnaire; U, unit.
*Nominal p≤0.05 and **nominal p≤0.005; p-values were not adjusted to control for multiplicity.

4.7.3.8 Secondary efficacy outcome: Change from baseline in AQLQ score

AQLQ score was assessed at Week 16 or early withdrawal. A significantly higher mean score was observed in the reslizumab 3.0 mg/kg group compared with placebo, and a numerical, but not significant, treatment effect was seen in the reslizumab 0.3 mg/kg group (Table 48). AQLQ scores for the 'symptoms' and 'emotional function' domains were also improved for both reslizumab groups compared with placebo. The results of a post hoc sensitivity analysis using all measurements without data exclusions for confounding medications were generally consistent with those based on the FAS.

Table 48: Change from baseline in AQLQ total score – full analysis set

	Reslizumab 0.3 mg/kg N=103	**Reslizumab 3.0 mg/kg N=103**	**Placebo N=105**
Baseline AQLQ score			
n	102	103	105
Mean (SD)	4.48 (1.23)	4.16 (1.22)	4.37 (1.20)
Change in AQLQ score at Week 16 or at last observed value			
n	96	99	101
LS mean (SE)	1.06 (0.19)	1.14 (0.18)	0.78 (0.18)
Treatment difference (SE), reslizumab – placebo	0.28 (0.16)	0.36 (0.16)	NA
95% CI	–0.04; 0.59	0.05; 0.67	NA
p-value	0.0822	0.0241	NA

Abbreviations: CI, confidence interval; AQLQ, Asthma quality of Life Questionnaire; L, litres; LS, least squares; NA, not applicable; SD, standard deviation; SE, standard error.

AQLQ responders

Compared with placebo ([redacted]%), the proportion of patients achieving at least a 0.5-point improvement in AQLQ score was [redacted] with reslizumab 3.0 mg/kg ([redacted]%, p=[redacted]) and numerically higher with reslizumab 0.3 mg/kg ([redacted]%, p=[redacted]; [redacted]28). The proportion of patients achieving at least a 0.5-point improvement in the domains of 'symptoms' and 'emotional function' was [redacted] for reslizumab 3.0 mg/kg versus placebo (p=[redacted] and p=[redacted], respectively)

Abbreviations: AQLQ, Asthma quality of Life Questionnaire; U, unit.
*Nominal p≤0.05; p-values were not adjusted to control for multiplicity.

4.7.3.9 Secondary efficacy outcome: Change from baseline in ASUI score

A significantly greater improvement (increase) in ASUI score over 16 weeks was observed in both the reslizumab 0.3 mg/kg and 3.0 mg/kg groups, compared with placebo (p=0.0094 and p=0.0160, respectively; Table 49). Improvements in asthma-related symptoms were seen at the first assessment visit in both reslizumab groups and were generally sustained throughout the treatment period (Figure 29).

The results of a post hoc sensitivity analysis using all measurements without data exclusions for confounding medications were consistent with those based on the FAS.

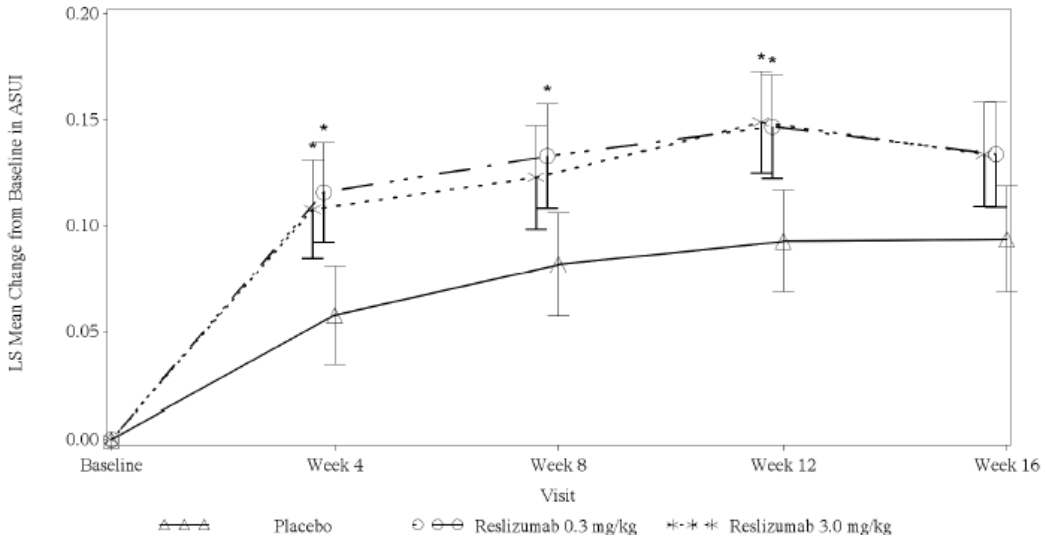
Table 49: Change from baseline in ASUI score – full analysis set

	Reslizumab 0.3 mg/kg N=103	**Reslizumab 3.0 mg/kg N=103**	**Placebo N=105**
Baseline ASUI score			
n	103	103	105
Mean (SD)	0.68 (0.21)	0.66 (0.19)	0.67 (0.19)
Change in ASUI score over 16 weeks			
n	101	101	103
LS mean (SE)	0.13 (0.02)	0.13 (0.02)	0.08 (0.02)
Treatment difference (SE), reslizumab – placebo	0.05 (0.02)	0.05 (0.02)	NA
95% CI	0.01; 0.09	0.01; 0.09	NA
p-value	0.0094	0.0160	NA

	Reslizumab 0.3 mg/kg N=103	Reslizumab 3.0 mg/kg N=103	Placebo N=105
Change in ASUI score at Week 16			
n	93	91	84
LS mean (SE)	0.13 (0.03)	0.13 (0.02)	0.94 (0.03)
Treatment difference (SE), reslizumab – placebo	0.04 (0.03)	0.04 (0.03)	NA
95% CI	–0.01; 0.09	–0.01; 0.09	NA
p-value	0.1177	0.1215	NA
Change in ASUI score at endpoint			
n	101	101	103
Mean (SD)	0.12 (0.21)	0.13 (0.23)	0.07 (0.20)

Abbreviations: ASUI, Asthma Symptom Utility Index; CI, confidence interval; LS, least squares; SD, standard deviation; SE, standard error.

Figure 29: Change from baseline in ASUI score – full analysis set



Abbreviations: ASUI, Asthma Symptom Utility Index. *Nominal p≤0.05 and **nominal p≤0.005; p-values were not adjusted to control for multiplicity. Data are LS means ± SE.

4.7.3.10 Secondary efficacy outcome: Change from baseline in SABA use

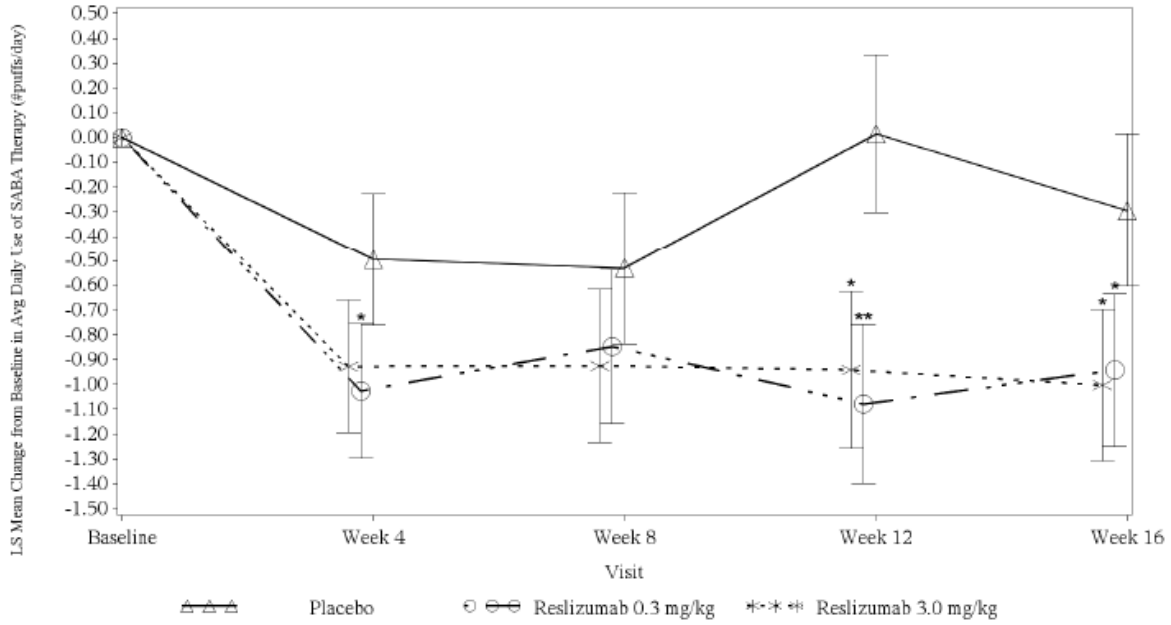
There was a significant improvement (decrease in daily use) in SABA use over 16 weeks in both reslizumab treatment groups compared with placebo (Table 50). The decrease in SABA requirement was observed for reslizumab-treated patients by the first assessment visit and was sustained throughout the study (Figure 30). The results of a post hoc sensitivity analysis using all measurements without data exclusions for confounding medications were consistent with those based on the FAS.

Table 50: Change from baseline in SABA use – full analysis set

	Reslizumab 0.3 mg/kg N=103	Reslizumab 3.0 mg/kg N=103	Placebo N=105
Baseline average daily SABA use			
n	103	103	104
Mean (SD)	1.9 (2.45)	2.3 (2.58)	2.3 (2.20)
Change in SABA use (puffs/day) over 16 weeks			
n	101	102	102
LS mean (SE)	–0.1 (0.28)	–0.9 (0.27)	–0.3 (0.28)
Treatment difference (SE), reslizumab – placebo	–0.65 (0.26)	–0.62 (0.26)	NA
95% CI	–1.15; –0.14	–1.13; –0.12	NA
p-value	0.0119	0.0151	NA
Change in SABA use (puffs/day) at Week 16			
n	93	91	83
LS mean (SE)	–0.9 (0.31)	–1.0 (0.30)	–0.3 (0.31)
Treatment difference (SE), reslizumab – placebo	–0.65 (0.32)	–0.71 (0.32)	NA
95% CI	–1.28; –0.02	–1.34; –0.08	NA
p-value	0.0442	0.0280	NA
Change in SABA use (puffs/day) at endpoint			
n	101	102	102
Mean (SD)	–0.7 (2.21)	–0.9 (3.13)	–0.1 (2.91)

Abbreviations: CI, confidence interval; LS, least squares; SABA, short-acting beta-agonist; SD, standard deviation; SE, standard error.

Figure 30: Change from baseline in SABA use – full analysis set



Abbreviations: SABA, short-acting beta-agonist.
*Nominal p≤0.05 and **nominal p≤0.005; p-values were not adjusted to control for multiplicity. Data are LS means ± SE.

4.7.3.11 Secondary efficacy outcome: Change from baseline in blood eosinophil count

There was a significantly greater reduction in blood eosinophil count over 16 weeks in both reslizumab treatment groups compared with placebo (Table 51 and [redacted]31).

Table 51: Change from baseline in blood eosinophil count – full analysis set

	Reslizumab 0.3 mg/kg N=103	Reslizumab 3.0 mg/kg N=103	Placebo N=105
Baseline blood eosinophil count,† cells/µL			
n	103	103	105
Mean (SD)	644 (492.6)	595 (393.1)	601 (433.1)
Change in eosinophil count over 16 weeks, cells/µL			
n	101	102	103
LS mean (SE)	–358 (27.7)	–529 (27.0)	–35 (27.1)
Treatment difference (SE), reslizumab – placebo	–323 (24.3)	–494 (24.2)	NA
95% CI	–370; –275	–542; –447	NA
p-value	0.0000	0.0000	NA
Change in eosinophil count at Week 16, cells/µL			
n	90	87	81
LS mean (SE)	–398 (31.3)	–538 (30.8)	–78 (31.0)

	Reslizumab 0.3 mg/kg N=103	Reslizumab 3.0 mg/kg N=103	Placebo N=105
Treatment difference (SE), reslizumab – placebo	–320 (32.0)	–460 (32.2)	NA
95% CI	–383; –257	–523; –396	NA
p-value	0.0000	0.0000	NA
Change in eosinophil count at endpoint, cells/µL			
n	102	103	103
Mean (SD)	–412 (474.6)	–493 (473.3)	–76 (509.5)

Abbreviations: CI, confidence interval; LS, least squares; SD, standard deviation; SE, standard error.
[†]Patients were required to have a blood eosinophil count ≥400/µL at least once during the screening period; however, as this value did not necessarily occur at baseline, baseline eosinophil counts for the randomised set include some patients with values <400/µL.

Significant treatment differences were also observed for both reslizumab doses at each assessment visit (Weeks 4, 8, 12 and 16; p=0.0000 for all comparisons). Data for the 90-day follow-up visit were [redacted] as the [redacted] ([redacted]%) of patients enrolled in the open-label extension study C38072/3085 or failed to provide follow-up for other reasons. In patients for whom data were available (n=[redacted] and [redacted] in the 0.3 mg/kg, 3.0 mg/kg and placebo groups, respectively), mean changes in blood eosinophil count (cells/µL) from baseline to the follow-up visit were [redacted] with reslizumab 0.3 mg/kg, [redacted] with reslizumab 3.0 mg/kg, and [redacted] with placebo. Thus, results from this small cohort indicate that blood eosinophils in both reslizumab groups [redacted] (i.e. approximately four months after the last treatment).

Horizontal bars indicate mean values.

4.7.3.12 Exploratory variables

Analyses of exploratory variables were not adjusted for multiplicity and thus p-values are nominal.

Sputum eosinophil count

Data on sputum eosinophils were available for [redacted] at both baseline and post-treatment, precluding meaningful analysis of any changes from baseline.

Biomarkers

Levels of eosinophil cationic protein (ECP) and eosinophil-derived neurotoxin (EDN) were analysed as indicators of eosinophilic inflammation. All available data were included for evaluation and missing or invalid results were not estimated. A [redacted] in the mean serum concentration of ECP and EDN was observed in both reslizumab groups from baseline to Week 16, indicating that the [redacted] in blood eosinophils with reslizumab treatment (Section 4.7.3.11) is accompanied by a [redacted] in these eosinophil granule proteins:

- ECP was [redacted] from [redacted] ng/mL to [redacted] ng/mL with reslizumab 0.3 mg/kg, from [redacted] ng/mL to [redacted] ng/mL with reslizumab 3.0 mg/kg, and from [redacted] ng/mL to [redacted] ng/mL with placebo.
- EDN was [redacted] from [redacted] ng/mL to [redacted] ng/mL with reslizumab 0.3 mg/kg, from [redacted] ng/mL to [redacted] ng/mL with reslizumab 3.0 mg/kg, and from [redacted] ng/mL to [redacted] ng/mL with placebo.

Analysis of eosinophilic peroxidase (EP) was [redacted]

Nasal polyps

Data on nasal polyps were available for only six patients at both baseline and post-treatment, precluding meaningful interpretation of any changes from baseline.

4.7.3.13 Efficacy conclusions

The results from C38072/3081 demonstrate that reslizumab at a dose of 0.3 mg/kg or 3.0 mg/kg, administered intravenously every 4 weeks over 16 weeks, is effective in improving lung function as assessed by FEV_1. The treatment effect is greater for the 3.0 mg/kg dose than for the 0.3 mg/kg dose.

Reslizumab 3.0 mg/kg also improves other measures of lung function (FVC, $FEF_{25–75\%}$ and % predicted FEV_1), asthma control (ACQ score), asthma symptoms (ASUI score), asthma QoL (AQLQ score) and rescue inhaler (SABA) use. Reslizumab 0.3 mg/kg produces similar improvements in asthma control, asthma symptoms and rescue inhaler use; however, this dose is not clearly effective in improving measures of lung function other than FEV_1, or in improving asthma QoL. Both reslizumab doses lead to a reduction in blood eosinophil level.

In summary, these results show that reslizumab 3.0 mg/kg provides the most robust efficacy, compared with a 0.3 mg/kg dose, in patients with asthma and elevated blood eosinophils (≥400/μL) inadequately controlled with medium to high dose ICS.

4.7.4 *Supporting studies*

Data are available from the Phase III study C38072/3084 (summarised below) to support the use of reslizumab in patients with asthma and elevated blood eosinophils.

Evidence on the sustained efficacy of reslizumab is also provided by the open-label extension study C38072/3085. As the primary focus of this trial was safety, it is reported in Section 4.12.2.

4.7.4.1 C38072/3084

The clinical objective of C38072/3084 was to characterise the efficacy of reslizumab in relation to baseline blood eosinophil levels, and thus eligibility for the study was not restricted by blood eosinophil level. Results for the subgroup of patients with baseline eosinophils ≥400 cells/µL are presented below for the primary endpoint and for secondary endpoints where data are available.

Methodology

Table 52: Design and methodology of C38072/3084

Study objective	**Primary objective** To characterise the efficacy of reslizumab treatment, at a dose of 3.0 mg/kg every 4 weeks for 16 weeks, in improving pulmonary function in relation to baseline blood eosinophil levels in patients with moderate to severe asthma. **Secondary objectives** • To characterise the efficacy of reslizumab treatment in relation to baseline blood eosinophil levels • To evaluate the safety, tolerability and immunogenicity of reslizumab treatment
Trial design	Phase III, multicentre, randomised, double-blind, placebo-controlled
Method of randomisation and blinding	Patients were randomised using IRT in a 4:1 ratio to receive either reslizumab or placebo. Randomisation was stratified by occurrence of asthma exacerbations during the previous year (yes/no). Patients and investigators remained blinded to treatment assignment during the study. The sponsor's clinical personnel were also blinded to study drug identity until the database was locked for analysis and the treatment assignment revealed.
Key inclusion criteria	• Adults aged 18–65 years with a diagnosis of asthma • ACQ score ≥1.5 • Airway reversibility of ≥12% to beta-agonist administration • Currently taking fluticasone at a dosage ≥440 µg daily (or equivalent) Stable baseline asthma therapy regimen for 30 days prior to screening • Negative pregnancy test for female subjects (unless surgically sterile or at least 2 years post-menopausal) • Females of childbearing potential must be using an accepted method of contraception and agree to continued use of this method during the study and for 30 days afterwards
Key exclusion criteria	• Confounding underlying lung disorder • Other pulmonary condition with symptoms of asthma and blood eosinophilia • Clinically meaningful comorbidity that would interfere with the study or compromise patient safety

	• Known hypereosinophilic syndrome • Has smoked within 6 months prior to screening • Use of systemic immunosuppressive, or immunomodulating, anti-IgE monoclonal antibody, methotrexate, cyclosporin, interferon-α, anti-TNF monoclonal antibody within 6 months prior to randomisation • Use of systemic (including oral) corticosteroids within 30 days prior to screening • Any aggravating, inadequately-controlled medical factors • Participation in any investigative drug or device study within 30 days prior to screening, and in any investigative biologics study within 90 days prior to screening • Previous treatment with reslizumab or other anti-hIL-5 monoclonal antibody • Pregnancy or lactation • Current infection or disease that may preclude assessment of asthma • History of concurrent immunodeficiency (HIV, AIDS or congenital immunodeficiency) • Suspected parasitic infestation/infection • Receipt of any live attenuated vaccine within 12-weeks prior to study
Settings and locations	103 centres in the USA
Duration of study	The study was conducted from February 2012 to August 2013. • Screening period: 3 weeks • Treatment period: 16 weeks • Follow-up period: 12 weeks
Trial drugs	• Reslizumab 3.0 mg/kg (N=398) • Placebo (N=98) Study drugs were administered by intravenous infusion once every 4 weeks for a total of 4 doses.
Prior and concomitant medications	Baseline asthma therapy regimen (including but not limited to ICS, leukotriene antagonists, 5-lipoxegnase inhibitors and cromolyn) was to be stable for 30 days before screening and to continue without dosage changes throughout the study, provided that these were started prior to the first dose of study drug and the patient had a diagnosis of asthma while taking them. Medications prohibited prior to screening (with corresponding washout times) and during the study were: • All other non-biologic investigational drugs (30 days) • Systemic (including oral) corticosteroids (30 days) • Live attenuated vaccines (12 weeks) • Any immunosuppressive or immunomodulatory agents, including but not limited to IgE monoclonal antibody, methotrexate, cyclosporin, and interferon-α (6 months) • Anti-TNF monoclonal antibody (6 months) • All other biologic therapies, including omalizumab (Xolair®; 6 months) • Anti-hIL-5 monoclonal antibody, including reslizumab, mepolizumab and benralizumab (no previous exposure allowed) Patients were to refrain from using SABAs for 6 hours, and LABAs for 12 hours, prior to any study visit.
Primary outcome	Change from baseline to Week 16 in FEV_1

Secondary outcomes	• Lung function as measured by FEV_1, % predicted FEV_1, FVC, and $FEV_{25–75\%}$ at Weeks 4, 8, 12, and 16 or early withdrawal • SABA use assessed at Weeks 4, 8, 12, and 16 or early withdrawal • Blood eosinophil count measured at Weeks 4, 8, 12, 16, and follow-up or early withdrawal • ACQ score assessed at Weeks 4, 8, 12, and 16 or early withdrawal
Pre-planned subgroups	As the clinical objective of C38072/3084 was to characterise the efficacy of reslizumab in relation to baseline blood eosinophil levels, the primary efficacy variable (FEV_1) and some of the secondary efficacy variables (FVC, ACQ score and SABA use) were analysed by baseline eosinophil count. The following cut-offs were used: • ≥400/µL and <400/µL • ≥300/µL and <300/µL • ≥200/µL and <200/µL • ≥100/µL and <100/µL For the primary efficacy analysis, the interaction between baseline blood eosinophils and lung function (FEV_1 at 16 weeks) was also analysed in the FEV_1 analysis set as defined below.
Populations analysed	• RS: All randomised patients, regardless of whether or not a patient received any study drug • FAS: All randomised patients treated with ≥1 dose of study drug[†] • SAS: All patients who received ≥1 dose of study drug • FEV_1 analysis set: The subpopulation of patients in the FAS with % predicted FEV_1 ≤85% at baseline
Statistical information	**Sample size** Approximately 500 patients were to be randomised, 400 in the reslizumab group and 100 in the placebo group). **Analysis of the primary efficacy outcome** Efficacy analyses were based on the FAS unless otherwise stated. A linear regression model was used to determine whether a relationship exists between baseline blood eosinophils and lung function (FEV_1 value at 16 weeks). The interaction was tested at the 0.1 significance level. The analysis was performed without imputation for missing data; the analysis was unbiased if the missing data mechanism was ignorable. Summary statistics of change from baseline to Week 16 in FEV_1 were provided by treatment group and baseline eosinophil category. Sensitivity analyses for the primary variable were conducted using 1) all FEV_1 measurements without data exclusions for confounding medications and 2) multiple imputation for missing data. A secondary analysis of the primary outcome measure was performed in the FEV_1 analysis set. **Analysis of secondary efficacy outcomes** Secondary efficacy outcomes were analysed using a MMRM, with the exception of SABA use which was summarised descriptively. The ACQ responder analysis was performed using the stratified Cochran Mantel Haenszel test. Change from baseline over 16 weeks for the key secondary outcomes of FEV_1 and ACQ was analysed using a sequential testing procedure at the 0.05 alpha level. Change from baseline to Weeks 4, 8, 12, 16 and endpoint was measured for the remaining secondary outcomes (ACQ, FVC, $FEF_{25–75\%}$, FEV_1, % predicted FEV_1, SABA use and blood eosinophil count) at the 0.05 alpha level. No adjustment for multiplicity was applied and thus p-values are nominal.

Abbreviations: ACQ, Asthma Control Questionnaire; AIDs, acquired immune deficiency syndrome; FAS, full analysis set; FEV_1, forced expiratory volume in one second; $FEV_{25–75\%}$, forced expiratory flow at 25–75% forced vital capacity; FVC, forced vital capacity; HIV, human immunodeficiency virus; ICS, inhaled corticosteroid; IRT, Interactive Response Technology; LABA, long-acting beta-agonist; MMRM, mixed-effect model for repeated measures; RS, randomised set; SABA, short-acting beta-agonist; SAS, safety analysis set. †Data on pulmonary function, SABA use, and ACQ, AQLQ and ASUI at a scheduled visit were excluded from the FAS if medications that could significantly confound interpretation of the efficacy parameters were used within 7 days prior to the assessment.

Patient disposition and baseline demographics

Patient disposition in C38072/3084 is presented in Figure 32.

The treatment groups were well balanced with regard to baseline demographics and characteristics (Table 53), with the exception that the proportion of females was slightly higher in the reslizumab group than the placebo group (66% and 55%, respectively).

Figure 32: CONSORT diagram for C38072/3084

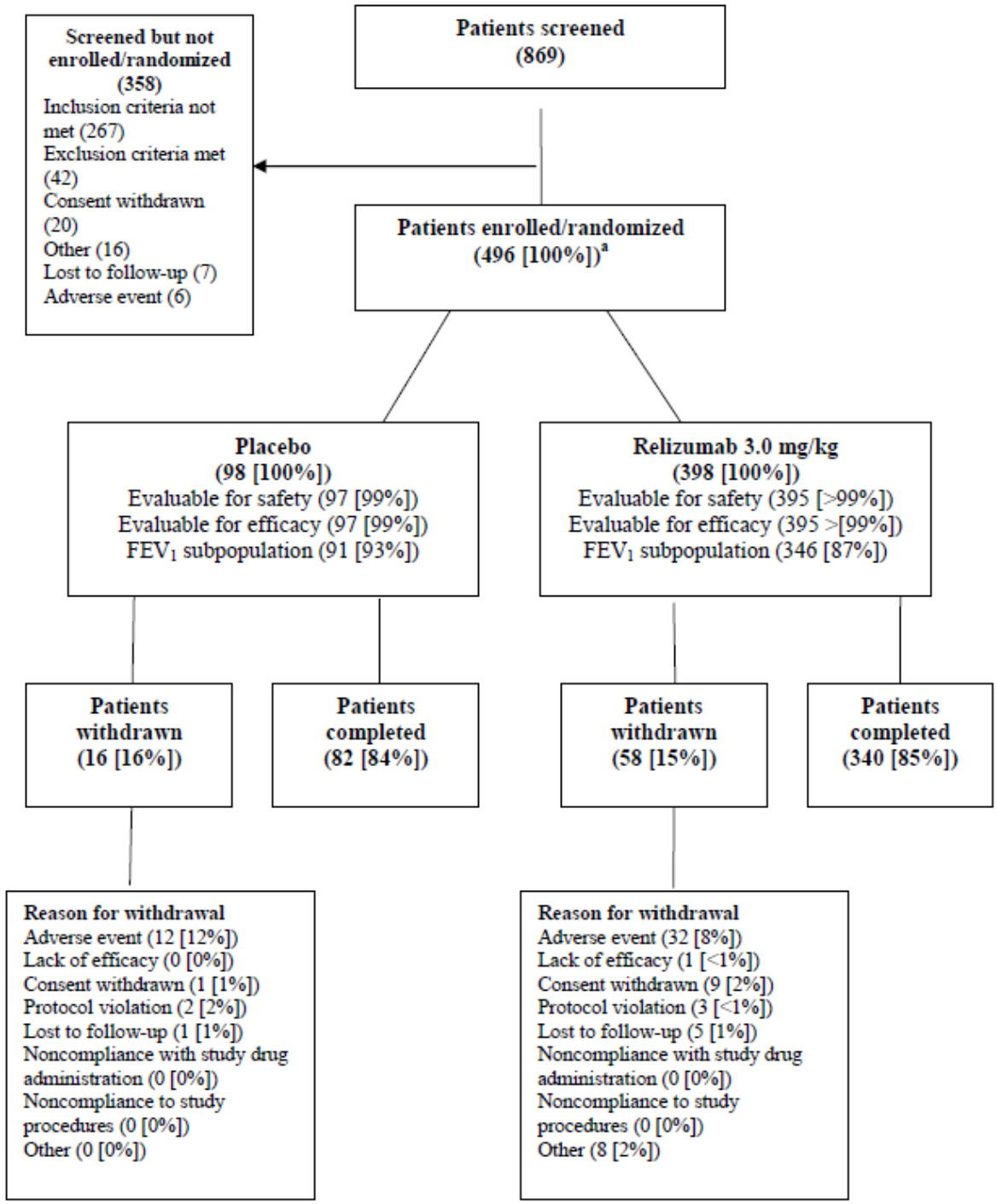


Table 53: Characteristics of participants in C38072/3084 across randomised groups – randomised set

Baseline characteristic	Reslizumab 3.0 mg/kg N=398	Placebo N=98
Age, years		
Mean (SD)	44.9 (12.00)	45.1 (13.38)
Gender		
Male, n (%)	137 (34)	44 (45)
Female, n (%)	261 (66)	54 (55)
Race, n (%)		
White	260 (65)	73 (74)
Black	113 (28)	21 (21)
Other	25 (6)	4 (4)
Height, cm		
Mean (SD)	167.7 (10.35)	169.7 (10.25)
BMI, kg/m^2		
Mean (SD)	32.3 (8.69)	31.6 (6.66)
Time since asthma diagnosis, years		
n	390	93
Mean (SD)	26.2 (15.69)	25.8 (16.75)
Asthma exacerbations in previous 12 months[†]		
Yes, n (%)	166 (42)	37 (38)
No, n (%)	231 (58)	61 (62)
Missing, n (%)	1 (<1)	0

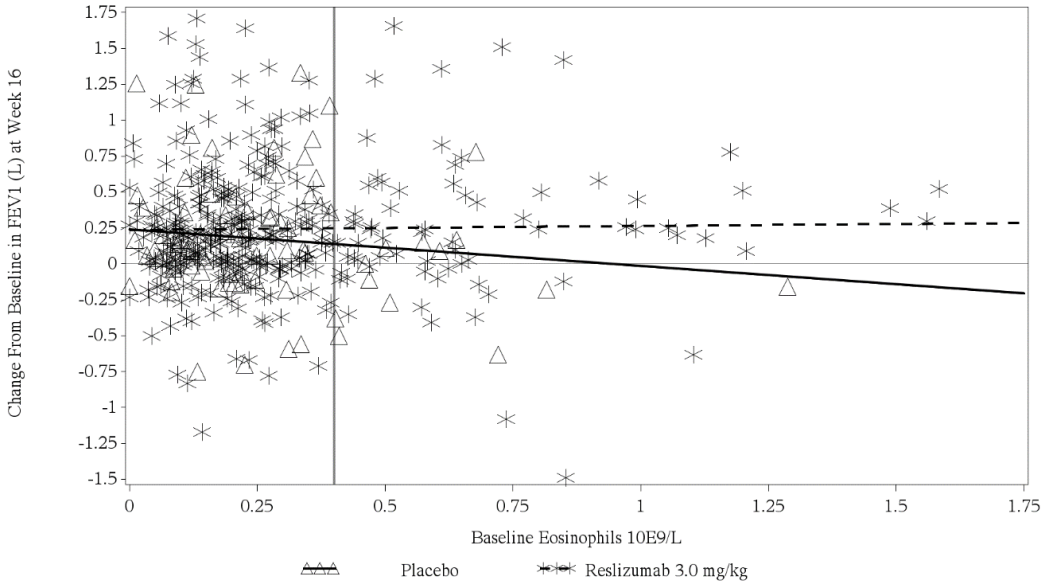
Abbreviations: BMI, body mass index; SD, standard deviation.
[†]CRF data; defined as any of the following: 1) a ≥20% reduction in FEV_1, 2) hospitalisation because of asthma, 3) emergency treatment because of asthma, or 4) use of prednisone or systemic corticosteroids for ≥3 days.
Data were available for all patients in the reslizumab (n=398) and placebo (n=98) groups unless otherwise stated.

Efficacy results

Primary efficacy outcome: Change from baseline to Week 16 in FEV_1

To determine whether a relationship exists between baseline blood eosinophils and lung function (FEV_1 at 16 weeks), the interaction between the two parameters was analysed by linear regression. This analysis failed to show a significant interaction; the slope difference (±SE) for reslizumab – placebo was 3.01±0.26 (p=0.2407; Figure 33).

Figure 33: Change from baseline in FEV_1 at Week 16 versus baseline eosinophil count – full analysis set



Abbreviations: FEV_1, forced expiratory volume in one second.

The results of a sensitivity analysis using all FEV_1 measurements without data exclusions for confounding medications were consistent with the primary analysis (slope difference of 0.31±0.26; p=0.2291). Sensitivity analysis using multiple imputation for missing data demonstrated an increase in slope difference (0.75±0.28; p=0.0086), indicating that the consideration of missing data would support a trend favouring an interaction between baseline eosinophils and the effect of reslizumab treatment.

A secondary analysis was also conducted for the subpopulation of patients with a baseline % predicted FEV_1 value of ≤85% (the FEV_1 analysis set); this yielded a slope difference that was consistent with the FAS (0.32±0.26; p=0.2246).

Change from baseline in FEV_1 by baseline blood eosinophil count (<400 µL or ≥400/µL) is presented in Table 54. In patients with a baseline eosinophil level ≥400/µL (the definition of eosinophilic asthma for the reslizumab Phase III confirmatory trials) there was a significant improvement in FEV_1 at Week 16 (p=0.0436), although the treatment effect in this subgroup was largely driven by a lack of effect in the 13 placebo patients. Baseline demographic data suggest that, compared with the reslizumab group, this small placebo cohort entered the study with more severe asthma (median ACQ score of 2.71 versus 2.29, and % predicted FEV_1 of 65% versus 67%). No significant treatment effect was observed at Week 16 in patients with baseline eosinophils <400/µL (p=0.5422) or in the overall population at Week 16 (p=0.1719) or over 16 weeks (p=0.0697). There was no obvious effect of blood eosinophil level on FEV_1 at cut-offs other than 400/µL.

Sensitivity analysis of change in FEV_1 by baseline eosinophil category and for the overall population using all FEV_1 measurements without data exclusions support the FAS analysis.

Table 54: Change from baseline in FEV_1 – full analysis set

	Baseline eosinophils ≥400/µL		Baseline eosinophils <400/µL		Overall population	
	Reslizumab 3.0 mg/kg N=77	Placebo N=19	Reslizumab 3.0 mg/kg N=317	Placebo N=76	Reslizumab 3.0 mg/kg N=395	Placebo N=97
Baseline FEV_1, L						
n	77	19	316	76	394	97
Mean (SD)	2.22 (0.81)	2.15 (0.61)	2.07 (0.66)	2.18 (0.65)	2.10 (0.69)	2.17 (0.63)
Change in FEV_1 at Week 16, L						
n	69	13	275	68	344	83
Mean (SD)	0.25 (0.52)	–0.07 (0.36)	0.24 (0.43)	0.22 (0.42)	0.25 (0.44)	0.18 (0.42)
LS mean (SE)	0.27 (0.06)	0.002 (0.12)	0.25 (0.03)	0.22 (0.05)	0.26 (0.02)	0.19 (0.04)
Treatment difference (SE), reslizumab – placebo	0.27 (0.13)		0.03 (0.05)		0.07 (0.05)	
95% CI	0.01; 0.53		–0.07; 0.14		–0.03; 0.17	
p-value	0.0436		0.5422		0.1719	

Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in one second; L, litres; LS, least squares; SD, standard deviation; SE, standard error.

Secondary efficacy outcomes

The results of secondary efficacy analyses are presented in Table 55 and summarised below. Analysis by blood eosinophil category was performed for FVC, ACQ score and SABA use only.

- Lung function as assessed by FVC was numerically improved (increased) with reslizumab versus placebo at Week 16 in the subgroup of patients with baseline eosinophils ≥400/μL (p=0.2675), but not in the <400/μL subgroup (p=0.8853). In the overall population, numerical increases in FVC were seen with reslizumab versus placebo at every visit (not shown); however, the treatment effect was not meaningful at Week 16 (p=0.8361) or over 16 weeks (p=0.1895). Similar to FEV_1, there was no obvious effect of blood eosinophil counts on FVC at cut-offs other than 400/μL.
- Lung function as assessed by $FEF_{25–75\%}$ was not analysed by eosinophil category. In the overall population, similar improvements (increases) from baseline were seen with reslizumab and placebo at Week 16 (p=0.5109) and over 16 weeks (p=0.5995).
- Change from baseline in % predicted FEV_1, another measure of lung function, was summarised descriptively for the overall population; a greater improvement (increase) was observed with reslizumab compared with placebo at Week 16.
- The effect of reslizumab treatment on improved asthma control tended to increase slightly with increasing baseline blood eosinophil level, with a substantial change observed at the 400/μL level (not shown). In patients with baseline eosinophils ≥400/μL, a numerical improvement (decrease) in ACQ score (–0.49) that approached the minimally important difference (MID) of the measure (–0.5) (105) was observed at Week 16 with reslizumab versus placebo (p=0.0643). At this timepoint there was no meaningful treatment effect in patients with baseline eosinophils <400/μL (p=0.2511), and a small but significant treatment effect in the overall population (p=0.0457).
- The proportion of patients in the overall population who achieved at least a 0.5-point improvement in ACQ score was numerically higher with reslizumab than placebo by Week 4; this treatment effect increased throughout the study, with significant differences seen at Weeks 12 and 16 (nominal p≤0.01).
- Treatment with reslizumab resulted in a substantial reduction in SABA use at Week 16 for patients with eosinophils ≥400/μL, compared with placebo, although this result was not significant (p=0.1264). No meaningful treatment effect was observed for the <400/μL subgroup at Week 16 (p=0.3484), or for the overall population at Week 16 (p=0.7589) or over 16 weeks (p=0.7468). There was no clear effect of blood eosinophil level on SABA use at cut-offs other than 400/μL.
- A significantly greater reduction from baseline in blood eosinophil count (cells/μL) was observed with reslizumab versus placebo in the overall population (p<0.0001 at Week 16 and over 16 weeks).

Table 55: Secondary efficacy outcomes – full analysis set

		Baseline eosinophils ≥400/µL		Baseline eosinophils <400/µL		Overall population	
		Reslizumab 3.0 mg/kg	Placebo	Reslizumab 3.0 mg/kg	Placebo	Reslizumab 3.0 mg/kg	Placebo
Change from baseline in FVC							
Baseline FVC, L	n	77	19	316	76	394	97
	Mean (SD)	3.32 (1.08)	3.21 (0.77)	2.97 (0.91)	3.22 (0.95)	3.04 (0.96)	3.21 (0.91)
Change in FVC at Week 16, L	n	69	13	275	68	344	83
	Mean (SD)	0.21 (0.66)	0.02 (0.39)	0.25 (0.48)	0.25 (0.41)	0.24 (0.52)	0.22 (0.42)
	LS mean (SE)	0.23 (0.07)	0.06 (0.14)	0.25 (0.03)	0.26 (0.05)	0.25 (0.03)	0.24 (0.05)
	Treatment difference (SE), reslizumab – placebo	0.18 (0.16)		–0.01 (0.06)		0.01 (0.06)	
	95% CI	–0.14; 0.49		–0.13; 0.11		–0.10; 0.12	
	p-value	0.2675		0.8853		0.8361	
Change from baseline in $FEF_{25–75\%}$							
Baseline $FEF_{25–75\%}$, L/second	n					391	95
	Mean (SD)					1.65 (0.91)	1.54 (0.67)
Change in $FEF_{25–75\%}$ at Week 16, L/second	n					341	81
	Mean (SD)					0.23 (0.89)	0.20 (0.51)
	LS mean (SE)					0.24 (0.04)	0.18 (0.09)
	Treatment difference (SE), reslizumab – placebo					0.06 (0.10)	
	95% CI					–0.13; 0.26	
	p-value					0.5109	

		Baseline eosinophils ≥400/µL		Baseline eosinophils <400/µL		Overall population	
		Reslizumab 3.0 mg/kg	Placebo	Reslizumab 3.0 mg/kg	Placebo	Reslizumab 3.0 mg/kg	Placebo
Change from baseline in % predicted FEV_1							
Baseline % predicted FEV_1	n					394	97
	Mean (SD)					66.8 (16.29)	66.1 (15.25)
Change in % predicted FEV_1 at Week 16	n					344	83
	Mean (SD)					7.8 (13.60)	5.5 (11.76)
Change from baseline in ACQ score							
Baseline ACQ score	n	77	19	316	76	394	97
	Mean (SD)	2.50 (0.74)	2.68 (0.74)	2.57 (0.69)	2.56 (0.68)	2.56 (0.70)	2.57 (0.69)
Change in ACQ score at Week 16	n	69	13	274	68	343	83
	Mean (SD)	–0.91 (0.99)	–0.58 (0.86)	–0.91 (0.78)	–0.75 (0.93)	–0.91 (0.83)	–0.70 (0.91)
	LS mean (SE)	–0.86 (0.11)	–0.37 (0.24)	–0.84 (0.05)	–0.71 (0.10)	–0.84 (0.05)	–0.65 (0.88)
	Treatment difference (SE), reslizumab – placebo	–0.49 (0.26)		–0.12 (0.11)		–0.20 (0.10)	
	95% CI	–1.01; 0.03		–0.33; 0.09		–0.39; –0.004	
	p-value	0.0643		0.2511		0.0457	
Change from baseline in SABA use							
Average SABA use at baseline	n	76	18	315	76	392	96
	Puffs/day, mean (SD)	1.9 (1.87)	2.2 (1.87)	1.9 (1.83)	2.0 (1.83)	1.9 (1.84)	2.0 (1.82)
Change in SABA use (puffs/day) at Week 16	n	69	12	274	68	343	82
	Mean (SD)	–0.9 (1.96)	0.1 (1.78)	–0.3 (1.87)	–0.5 (2.03)	–0.4 (1.90)	–0.4 (1.98)

		Baseline eosinophils ≥400/µL		Baseline eosinophils <400/µL		Overall population	
		Reslizumab 3.0 mg/kg	Placebo	Reslizumab 3.0 mg/kg	Placebo	Reslizumab 3.0 mg/kg	Placebo
	LS mean (SE)	–0.80 (0.19)	–0.09 (0.43)	–0.22 (0.11)	–0.44 (0.21)	–0.34 (0.10)	–0.41 (0.19)
	Treatment difference (SE), reslizumab – placebo	–0.71 (0.46)		0.22 (0.23)		0.06 (0.21)	
	95% CI	–1.62; 0.20		–0.24; 0.67		–0.34; 0.47	
	p-value	0.1264		0.3484		0.7589	
Change from baseline in blood eosinophil count							
Baseline blood eosinophil count, cells/µL	n					394	95
	Mean (SD)					280 (245.4)	279 (221.3)
Change in blood eosinophil count at Week 16, cells/µL	n					346	80
	Mean (SD)					–239 (246.2)	21 (246.6)
	LS mean (SE)					–237 (6.7)	16 (13.2)
	Treatment difference (SE), reslizumab – placebo					–254 (14.6)	
	95% CI					–282; –225	
	p-value					<0.0001	

Abbreviations: ACQ, Asthma Control Questionnaire; CI, confidence interval; $FEF_{25–75\%}$, forced expiratory flow at 25–75% forced vital capacity; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; L, litres; LS, least squares; SABA, short-acting beta-agonist; SD, standard deviation; SE, standard error.
Grey cells indicate endpoints for which data were reported for the overall population only.

4.8 *Subgroup analysis*

Pre-planned subgroup analyses for the primary and secondary efficacy outcomes in studies 3082, 3083, 3081, and the supportive study 3084, are reported in Section 4.7 along with the results for the FAS.

In the population of adult patients with severe eosinophilic asthma (GINA 4/5), [redacted] of the [redacted] patients on reslizumab 3mg/kg ([redacted]%) and [redacted] of the [redacted] patients ([redacted]%) on placebo were on OCS at baseline. In the group on baseline OCS in the reslizumab 3 mg/kg arm there were [redacted] patients ([redacted]%) with [redacted] during the study period compared to [redacted] patients ([redacted]%) on placebo. Nearly all of these were treated with 3 or more days of further OCS (except one in each group). The CAE rate ratio in this group was [redacted] ([redacted]) p<[redacted], giving a [redacted] of exacerbations of [redacted]%. In the group not on baseline OCS in the reslizumab 3mg/kg arm there were [redacted] patients ([redacted]%) with [redacted] during the study period compared to [redacted] patients ([redacted]%) on placebo. The CAE rate ratio in this group was [redacted] ([redacted]% CI: [redacted]) p<[redacted], giving a [redacted] of exacerbations of [redacted]%.

4.9 *Meta-analysis*

As described in Section 4.1, a SLR was conducted to identify evidence of the efficacy and safety of reslizumab versus BSC in adult patients with severe eosinophilic asthma. The results from studies of reslizumab versus BSC (placebo arm) identified through the SLR were pooled and meta-analyses were performed for each outcome.

4.9.1 *Methodology*

4.9.1.1 Study selection and outcomes

Only RCTs reporting at least one outcome of interest were included in the meta-analyses. The complete list of endpoints of interest and the feasibility assessment of the analysis of each endpoint is provided in Appendix 3. Only publications in English were included. Seven outcomes of interest were included as defined as the main outcomes of interest in the trials:

- **Efficacy outcomes:** Change from baseline in FEV_1, change from baseline in ACQ, change from baseline in AQLQ, rate of clinically significant exacerbations, number of patients hospitalised due to exacerbations
- **Safety outcomes:** Serious adverse events, discontinuation due to adverse events

All RCTs included in the analysis evaluated reslizumab 3.0 mg/kg versus BSC (placebo arm). According to the BTS/SIGN guidelines (22), BSC relies on the use of a Personal Asthma Action Plan (PAAP), the avoidance of environmental/dietary triggers and the use of recommended medications. A summary of the key components of the PAAP as defined by the BTS is provided in Appendix 3.

4.9.1.2 Data extraction

Data from the included reslizumab RCTs were extracted into a tabular summary in Microsoft Excel. A second reviewer performed a quality check on data extracted from

20% of the publications. A statistical analyst performed a quality check of all data used as inputs for the meta-analysis.

Descriptive statistics were used to describe the main study and patient characteristics for each selected trial. The following characteristics were analysed:

- **Study design:** Blinding of the trial, allowed concomitant therapies (ICS, LABA, SABA, OCS)
- **General characteristics:** Age at baseline, proportion of males/females, weight at baseline, ethnicity/race, definition of exacerbation, baseline IgE serum concentration, asthma phenotype
- **Medical characteristics:** Duration of asthma (time since first diagnosis), severity of asthma at baseline (GINA or BTS/SIGN treatment step); FEV_1 at baseline, number of exacerbations during the year preceding trial enrolment; ACQ and AQLQ scores at baseline, ASUI score at baseline, concomitant use of OCS

One of the main challenges of meta-analysis is to assess the comparability between trials. 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. The following potential treatment effect modifiers were assessed across the trials included in the meta-analysis:

- Presence of inflammatory phenotype asthma
- Presence of early-onset allergic asthma
- Presence of late-onset eosinophilic asthma
- Presence of specific biomarkers (related to biologic therapies, i.e. baseline IgE serum concentration)
- Obesity
- Frequent severe exacerbation
- OCS use
- Lung function parameters (FEV_1)
- Symptoms at baseline (level of control)

4.9.1.3 Statistical methods

Data inputs

For binary outcomes, the number of events and total number of patients in each treatment arm were used as inputs for the statistical model. For continuous outcomes, the absolute difference between treatment arms in mean changes from baseline and SE were used as inputs. For rate outcomes, counts over a certain time period (which could vary between different trials) were used. As recommended in the NICE Decision Support Unit (DSU) Technical Support Document (106), the total number of person-years at risk was used rather than the denominator number at risk.

Missing data

If absolute differences between treatment arms were not reported but the values at endpoint were reported, they were imputed as follows:

$$Absolute\ difference\ between\ treatment\ arms = value\ at\ endpoint_{arm\ 1} - value\ at\ endpoint_{arm\ 2}$$

If absolute differences between treatment arms were not reported but the absolute differences from baseline were reported, they were imputed as follows:

$$Absolute\ difference\ between\ treatment\ arms = absolute\ change\ from\ baseline_{arm\ 1} - absolute\ change\ from\ baseline_{arm\ 2}$$

If absolute difference from baseline were not reported for each treatment arm, they were imputed as follows:

$$Absolute\ change\ from\ baseline = Mean\ value\ at\ endpoint - Mean\ value\ at\ baseline$$

The variance of this absolute change from baseline was estimated as follows:

$$\sigma_{change}{}^2 = \sigma_{final}{}^2 + \sigma_{baseline}{}^2 - 2\rho\sqrt{\sigma_{final}{}^2 * \sigma_{baseline}{}^2}$$

The variance of the mean change from baseline of the comparator arm was required to compute the overall variance of the estimate. If the variance could not be estimated using the formula above because the SD at baseline was missing, then this SD was imputed using the mean value of SDs from the arms of the other studies (107).

In the event of missing dispersion information, dispersion for the change from baseline was imputed using the p-value for the difference in change from baseline between intervention arms. The t value was first obtained given the corresponding z score and degrees of freedom. The SE for the difference in means (MD) was then imputed as follows:

$$SE = \frac{MD}{t}$$

When the MD was not reported directly, it was calculated based on the difference in change from baseline between the treatment arms. The corresponding SDs were then computed using the number of patients allocated to each treatment arm (N_E and N_C):

$$SD = \frac{SE}{\sqrt{\frac{1}{N_E} + \frac{1}{N_C}}}$$

The SE for individual treatment arms was imputed as follows:

$$SE = \frac{SD}{\sqrt{N}}$$

Finally, for the analysis of rates, the number of events occurring in arm k of trial i during the trial follow-up period and the exposure time in person-years were both required as inputs to conduct the analysis in WinBUGS. When only rates were reported, the number of events occurring in arm k of trial j during the trial follow-up period was imputed as follows:

$$Exacerbation\ rate\ = \frac{Number\ of\ exacerbations}{Person - years}$$

where

$$Number\ of\ exacerbations = Exacerbation\ rate\ \times follow - up\ time$$

and

$$Person - years = Number\ of\ patients\ \times follow - up\ time\ in\ years$$

Model

A frequentist model (108) was used as it is the standard approach for direct comparisons. Results obtained with both random and fixed-effects models are presented in Section 4.9.2. For the interpretation of results, the random-effects model was used if there was unexplained heterogeneity. Otherwise, results were interpreted based on a fixed-effects model.

The inverse variance-weighted method was used to analyse binary and continuous outcomes (this is the standard approach) (109). The weights used to pool the different studies were the inverse of the variance of the study outcomes. The weighted least squares method (the most commonly used method) was used to estimate the between-study variance for the random-effects model.

In the case of binary outcomes, the inverse variance-weighted method could not be implemented if one or more arms in one or more studies reported zero events. The presence of zero(s) in the analysis of an outcome was handled using the Mantel-Haenszel method, as recommended in the Cochrane handbook.

A Bayesian framework was adopted for the analysis of rates of clinically significant exacerbations. Model selection could not be handled in the same fashion as for other binary outcomes mainly because follow-up times varied considerably across trials. Based on NICE recommendations (106), rates of clinically significant exacerbations were modelled using a Poisson likelihood and a log link, where the number of person-years at risk was used rather than the number of patients at risk. As such, exacerbation rates were adjusted based on their associated follow-up times allowing the consistency assumption required to pool the findings of different studies to be preserved.

Given the lack of consensus for modelling the Poisson likelihood in the frequentist framework, a Bayesian framework was adopted following the guidance published by the NICE DSU (106) and using its examples of WinBUGS model specifications. The use of non-informative priors in the Bayesian model meant that the results obtained were completely driven by the data and highly similar to those that would have been obtained if a frequentist framework had been adopted.

The relative goodness of fit of the models was assessed using the deviance information criterion (DIC). The fixed-effects and random-effects models were performed and the one associated with the lowest DIC was selected (with a difference of at least three points in DIC) (110). The model with the smallest DIC is the model with the best compromise between adequacy and complexity.

$$DIC = \overline{D} + P_D$$

Where $\overline{D}$ is the posterior mean residual deviance and P_D is the effective number of parameters.

The posterior mean residual deviance $\overline{D}$ was used to assess the absolute goodness of fit of the model. For a model that fits well, $\overline{D}$ approximates the number of unconstrained data points (111). When the random-effects model was selected according to the DIC, the results of the fixed-effects model were reported as a sensitivity analysis.

Heterogeneity assessment

For each pairwise comparison, Cochran's Q test was conducted and the I^2 statistic was calculated. Heterogeneity was suspected if the Cochran's Q test was significant with a significance level of 10%, or I^2 was greater than 50% (112).

A forest plot was generated to depict heterogeneity (if I^2 >50% or the p-value of the Cochran's Q test <10%). However, based on power calculations performed by Valentine et al (113), the Cochran's Q test is not considered to be a reliable test for assessing heterogeneity when less than five studies are used as inputs for direct comparisons.

4.9.2 *Results*

Results from the direct treatment comparisons of reslizumab 3.0 mg/kg versus BSC/placebo (meta-analyses of trial results) are presented for both 16±4 and 52±4 weeks follow-up. The reslizumab trials included in the analysis are listed in Table 12 in Section 4.2. Details of data for each endpoint that were available from these trials are presented in Table 56.

Table 56: Studies included for the analysis of each endpoint

Outcome	Trials providing data for follow-up period	
	16±4 weeks	52±4 weeks
FEV_1	Castro et al, 2011 (Res-5-0010) Study 3081 Study 3082 Study 3083 Study 3084	Study 3082 Study 3083
ACQ	Castro et al, 2011 (Res-5-0010) Study 3081 Study 3082 Study 3083 Study 3084	N/A
AQLQ	Study 3081	Study 3082

Outcome	Trials providing data for follow-up period	
	16±4 weeks	52±4 weeks
	Study 3082 Study 3083	Study 3083
Clinically significant exacerbations†	Castro et al, 2011 (Res-5-0010) Study 3082 Study 3083	
Hospitalisations	Castro et al, 2011 (Res-5-0010)	Study 3082 Study 3083
Discontinuation due to AEs	Castro et al, 2011 (Res-5-0010) Study 3081 Study 3082 Study 3083 Study 3084	Study 3082 Study 3083
SAEs	Castro et al, 2011 (Res-5-0010) Study 3081 Study 3084	Study 3082 Study 3083

Abbreviations: ACQ, Asthma Control Questionnaire; AE, adverse event; AQLQ; Asthma Quality of Life Questionnaire; FEV_1, forced expiratory volume in one second; N/A, not applicable; SAE, serious adverse event. †The analysis of exacerbation rates already takes time of assessment into account, so is not reported by time point.

4.9.2.1 Change from baseline in FEV_1 at 16±4 weeks

The inputs used in the direct comparison of reslizumab versus placebo are shown in Table 57. Differences in changes from baseline in FEV_1 were observed across the placebo arms of the trials, most notably between Res-5-0010 (–0.08 L/second) and Study 3084 (0.18 L/second). Moreover, there was significant variation in the change from baseline in FEV_1 in the placebo arm of Study 3084 (SE of 0.466).

Table 57: Change from baseline in FEV_1 at 16±4 weeks: Reslizumab 3.0 mg/kg versus placebo direct comparison inputs

Study and follow-up period	Treatment arm	N	Change from baseline in FEV_1, L/second			
			Mean	SE	SD	Notes
Castro et al, 2011 (Res-5-0010) (15 weeks)	Reslizumab	53	0.18		0.372	SE imputed from SD for statistical analysis
	Placebo	53	–0.08		0.413	
Study 3082 (16 weeks)	Reslizumab	232	0.199	0.0274	0.417	Change to Week 16 (mean)
	Placebo	228	0.13	0.0254	0.383	
Study 3083 (16 weeks)	Reslizumab	214	0.247	0.0306	0.448	Change at Week 16 (mean)
	Placebo	214	0.151	0.0292	0.427	
Study 3081 (16 weeks)	Reslizumab	91	0.243	0.0501	0.478	Change at 16 weeks (mean)
	Placebo	84	0.052	0.043	0.394	
Study 3084 (16 weeks)	Reslizumab	344	0.245	0.0241	0.442	Change at 16 weeks (mean)
	Placebo	83	0.18	0.466	0.424	

Abbreviations: FEV_1, forced expiratory volume in one second; SD, standard deviation; SE, standard error.

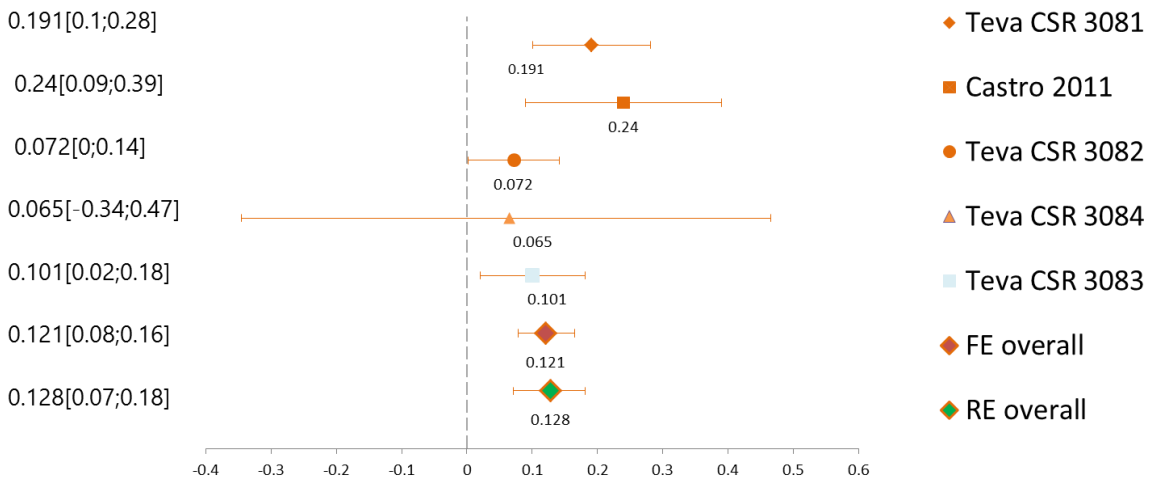
The results of the direct comparison showed that there was a significantly greater improvement (increase) in FEV_1 with reslizumab versus placebo (Table 58). Moderate heterogeneity (41%) was detected by the I^2 test and is depicted in Figure 34.

Table 58: Change from baseline in FEV_1 at 16±4 weeks: Results from direct comparison of reslizumab 3.0 mg/kg versus placebo

	Difference between means, reslizumab versus placebo (95% CI)
Fixed-effects model	0.12 (0.08; 0.16)
Random-effects model	0.13 (0.07; 0.18)
P-value of the Cochran test	0.15
I^2	41%

Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in one second.
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.

Figure 34: Change from baseline in FEV_1 at 16±4 weeks: Forest plot for the heterogeneity assessment of reslizumab versus placebo



Abbreviations: FE, fixed effects; FEV_1, forced expiratory volume in one second; RE, random effects.

4.9.2.2 Change from baseline in FEV_1 at 52±4 weeks

The inputs used in the direct comparison of reslizumab versus placebo are shown in Table 59.

Table 59: Change from baseline in FEV_1 at 52±4 weeks: Reslizumab 3.0 mg/kg versus placebo direct comparison inputs

Study and follow-up period	Treatment arm	N	Change from baseline in FEV_1, L/second			
			Mean	SE	SD	Notes
Study 3082 (52 weeks)	Reslizumab	243	0.24	0.029	0.457	Change to Week 52 (mean)
	Placebo	241	0.08	0.027	0.417	
Study 3083	Reslizumab	230	0.23	0.028	0.432	Change at Week 52

Study and follow-up	Treatment	N	Change from baseline in FEV_1, L/second			
(52 weeks)	Placebo	227	0.12	0.027	0.402	(mean)

Abbreviations: FEV_1, forced expiratory volume in one second; SD, standard deviation; SE, standard error.

The results of the direct comparison showed that there was a significantly greater improvement (increase) in FEV_1 with reslizumab versus placebo (Table 60). No heterogeneity was detected by the I^2 test.

Table 60: Change from baseline in FEV_1 at 52±4 weeks: Results from direct comparison of reslizumab 3.0 mg/kg versus placebo

	Difference between means, reslizumab versus placebo (95% CI)
Fixed-effects model	0.13 (0.08; 0.18)
Random-effects model	0.13 (0.08; 0.18)
P-value of the Cochran test	0.67
I^2	0%

Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in one second.
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.

4.9.2.3 Change from baseline in ACQ score at 16±4 weeks

The inputs used in the direct comparison of reslizumab versus placebo are shown in Table 61.

Table 61: Change from baseline in ACQ at 16±4 weeks: Reslizumab 3.0 mg/kg versus placebo direct comparison inputs

Study and follow-up period	Treatment arm	N	Change from baseline in ACQ score			
			Mean	SE	SD	Notes
Castro, 2011 (Res-5-0010) (15 weeks)	Reslizumab	53	–0.700		1.020	SE imputed from SD for statistical analysis
	Placebo	53	–0.300		1.010	
Study 3082 (16 weeks)	Reslizumab	232	–1.005	0.068	1.037	Change to Week 16 (mean)
	Placebo	228	–0.887	0.066	0.998	
Study 3083 (16 weeks)	Reslizumab	214	–1.020	0.071	1.039	Change at Week 16 (mean)
	Placebo	214	–0.804	0.068	0.991	
Study 3081 (16 weeks)	Reslizumab	91	-0.989	0.119	1.192	Change to endpoint (mean)
	Placebo	84	-0.531	0.101	1.025	
Study 3084 (16 weeks)	Reslizumab	344	-0.912	0.045	0.825	Change at 16 weeks (mean)
	Placebo	83	-0.701	0.100	0.914	

Abbreviations: ACQ, Asthma Control Questionnaire; SD, standard deviation; SE, standard error.

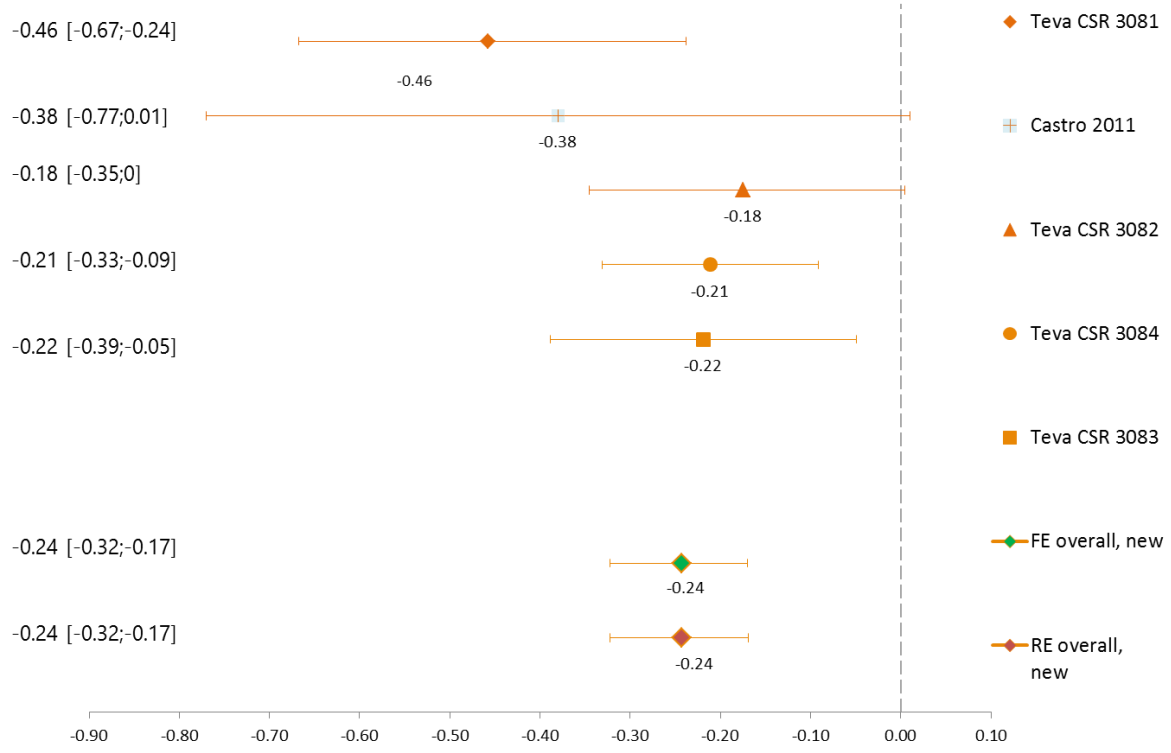
The results of the direct comparison showed that there was a significantly greater improvement (decrease) in ACQ score with reslizumab versus placebo (Table 62). Mild heterogeneity (24%) was detected by the I^2 test and is depicted in Figure 35.

Table 62: Change from baseline in ACQ at 16±4 weeks: Results from direct comparison of reslizumab 3.0 mg/kg versus placebo

	Difference between means, reslizumab versus placebo (95% CI)
Fixed-effects model	–0.24 (–0.32; –0.17)
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. I^2 is based on the Q statistic from the Cochran test and is a measure of heterogeneity.

Figure 35: Change from baseline in ACQ at 16±4 weeks: Forest plot for the heterogeneity assessment of reslizumab 3.0 mg/kg versus placebo



Abbreviations: ACQ, Asthma Control Questionnaire; FE, fixed-effects; RE, random-effects.

4.9.2.4 Change from baseline in AQLQ score at 16±4 weeks

The inputs used in the direct comparison of reslizumab versus placebo are shown in Table 63. Larger least squares (LS) mean standard errors were reported in Study 3081 than in the other reslizumab trials.

Table 63: Change from baseline in AQLQ at 16±4 weeks: Reslizumab 3.0 mg/kg versus placebo direct comparison inputs

Study and follow-up period	Treatment arm	N	Change from baseline in AQLQ score			
			Mean	SE	SD	Notes
Study 3082 (16 weeks)	Reslizumab	232	1.03	0.0791	1.1946	Change to Week 16 (mean)
	Placebo	228	0.866	0.0758	1.1465	
Study 3083 (16 weeks)	Reslizumab	214	0.949	0.0751	1.0957	Change to Week 16 (mean)
	Placebo	214	0.789	0.0773	1.1354	
Study 3081 (16 weeks)	Reslizumab	91	1.138	0.183		Mean not available for change at 16 weeks
	Placebo	84	0.779	0.182		LS mean

Abbreviations: AQLQ, Asthma Quality of Life Questionnaire; LS, least squares; SD, standard deviation; SE, standard error.

The results of the direct comparison showed that there was a significantly greater improvement (increase) in AQLQ score with reslizumab versus placebo (Table 64). No heterogeneity was detected by the I^2 test.

Table 64: Change from baseline in AQLQ at 16±4 weeks: Results from direct comparison of reslizumab 3.0 mg/kg versus placebo

	Difference between means, reslizumab versus placebo (95% CI)
Fixed-effects model	0.24 (0.12; 0.36)
Random-effects model	0.24 (0.12; 0.36)
P-value of the Cochran test	0.77
I^2	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.

4.9.2.5 Change from baseline in AQLQ score at 52±4 weeks

The inputs used in the direct comparison of reslizumab versus placebo are shown in Table 65.

Table 65: Change from baseline in AQLQ at 52±4 weeks: Reslizumab 3.0 mg/kg versus placebo direct comparison inputs

Study and follow-up period	Treatment arm	N	Change from baseline in AQLQ score			
			Mean	SE	SD	Notes
Study 3082 (52 weeks)	Reslizumab	245	1.30	0.078	1.191	–
	Placebo	244	1.01	0.079	1.201	
Study 3083 (52 weeks)	Reslizumab	232	1.10	0.078	1.149	–
	Placebo	232	0.90	0.080	1.197	

Abbreviations: AQLQ, Asthma Quality of Life Questionnaire; SD, standard deviation; SE, standard error.

The results of the direct comparison showed that there was a significantly greater improvement (increase) in AQLQ score with reslizumab versus placebo (Table 66). No heterogeneity was detected by the I^2 test.

Table 66: Change from baseline in AQLQ at 52±4 weeks: Results from direct comparison of reslizumab 3.0 mg/kg versus placebo

	Difference between means, reslizumab versus placebo (95% CI)
Fixed-effects model	0.33 (0.19; 0.46)
Random-effects model	0.33 (0.19; 0.46)
P-value of the Cochran test	0.51
I^2	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.

4.9.2.6 Clinically significant exacerbations

The inputs used in the direct comparison of reslizumab versus placebo are shown in Table 67. The number of exacerbations and person-years was calculated as described in Section 4.9.1, except for the Res-5-0010 trial where only the proportion of patients with exacerbations was reported (rather than exacerbation rates).

Table 67: Clinically significant exacerbations: Reslizumab 3.0 mg/kg versus placebo direct comparison inputs

Study	Treatment arm	N	Exacerbation rate	Number of exacerbations	Person-years
Castro, 2011 (Res-5-0010) *(over 15 weeks)*	Reslizumab	53	NA	4	15.29
	Placebo	53	NA	10	15.29
Study 3082 *(over 52 weeks)*	Reslizumab	243	0.90	47	243.00
	Placebo	241	1.80	94	241.00
Study 3083 *(over 52 weeks)*	Reslizumab	230	0.86	45	230.00
	Placebo	227	2.11	110	227.00

Abbreviations: N/A, not applicable.

The analysis of clinically significant exacerbation rates was performed within a Bayesian framework, as recommended by the NICE DSU (106). Statistically significant results were obtained with the fixed-effects model, with a Bayesian probability of 100% (i.e. reslizumab always performs better than placebo) (Table 68). Given the small number of trials included in the analysis, the credibility interval associated with the random-effects model included 1, although reslizumab was still associated with a probability of performing better than placebo of 97%.

Table 68: Clinically significant exacerbations: Results from the direct comparison of reslizumab 3.0 mg/kg versus placebo

	Median HR (95% CI)	Probability	DIC

	Median HR (95% CI)	Probability	DIC
Fixed-effects model	0.44 (0.35; 0.56)	100%	78.06
Random-effects model	0.43 (0.17; 1.10)	97%	78.81

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

4.9.2.7 Patients hospitalised due to exacerbations at 16±4 weeks

The direct comparison of reslizumab with placebo at 16±4 weeks relied on only one trial (Res-5-0010) reporting a very small number of events. Results from this trial are presented in Table 69.

Table 69: Patients hospitalised due to exacerbations at 16±4 weeks in Res-5-0010: Reslizumab 3.0 mg/kg versus placebo

Study and follow-up period	Treatment arm	N	Number of events	% of patients hospitalised
Castro, 2011 (Res-5-0010) (15 weeks)	Reslizumab	53	1	1.9
	Placebo	53	0	0.0

4.9.2.8 Patients hospitalised due to exacerbations at 52±4 weeks

The inputs used in the direct comparison of reslizumab versus placebo are shown in Table 70.

Table 70: Patients hospitalised due to exacerbations at 52±4 weeks: Reslizumab 3.0 mg/kg versus placebo direct comparison inputs

Study and follow-up period	Treatment arm	N	Number of patients hospitalised
Study 3082 (52 weeks)	Reslizumab	243	9
	Placebo	241	11
Study 3083 (52 weeks)	Reslizumab	230	5
	Placebo	227	8

Few patients were hospitalised over the course of the trials. Results from the direct comparison of reslizumab versus placebo were not statistically significant (Table 71).

Table 71: Patients hospitalised due to exacerbations at 52±4 weeks: Results from direct comparison of reslizumab 3.0 mg/kg versus placebo

	Difference between means, reslizumab versus placebo (95% CI)
Fixed-effects model	0.73 (0.36; 1.47)
Random-effects model	0.73 (0.36; 1.47)
P-value of the Cochran test	0.72
I^2	0%

Abbreviations: CI, confidence interval.
An OR <1 indicates that reslizumab is better than placebo. Statistical significance is reached when the 95% CI excludes 1. I^2 is based on the Q statistic from the Cochran test and is a measure of heterogeneity.

4.9.2.9 Discontinuation due to adverse events at 16±4 weeks

The inputs used in the direct comparison of reslizumab versus placebo are shown in Table 72.

Table 72: Discontinuation due to AEs at 16±4 weeks: Reslizumab 3.0 mg/kg versus placebo direct comparison inputs

Study and follow-up period	Treatment arm	N	% of patients who discontinued due to AEs
Castro, 2011 (Res-5-0010) (15 weeks)	Reslizumab	53	0
	Placebo	53	1.8
Study 3081 (16 weeks)	Reslizumab	103	1.09
	Placebo	105	0
Study 3084 (16 weeks)	Reslizumab	395	0.87
	Placebo	97	1.2

Abbreviations: AE, adverse event.

The results of the direct comparison were not statistically significant (Table 73).

Table 73: Discontinuation due to AEs at 16±4 weeks: Results from direct comparison of reslizumab 3.0 mg/kg versus placebo

	Difference between means, reslizumab versus placebo (95% CI)
Fixed-effects model	0.83 (0.17; 4.16)
Random-effects model	0.83 (0.17; 4.16)
P-value of the Cochran test	0.64
I^2	0%

Abbreviations: AE, adverse event; CI, confidence interval.
An OR <1 indicates that reslizumab is better than placebo. Statistical significance is reached when the 95% CI excludes 1. I^2 is based on the Q statistic from the Cochran test and is a measure of heterogeneity.

4.9.2.10 Discontinuation due to adverse events at 52±4 weeks

The inputs used in the direct comparison of reslizumab versus placebo are shown in Table 74.

Table 74: Discontinuation due to AEs at 52±4 weeks: Reslizumab 3.0 mg/kg versus placebo direct comparison inputs

Study and follow-up period	Treatment arm	N	% of patients who discontinued due to AEs
Study 3082 (52 weeks)	Reslizumab	243	2.0
	Placebo	241	3.0
Study 3083 (52 weeks)	Reslizumab	230	3.0

Study and follow-up period	Treatment arm	N	% of patients who discontinued due to AEs
	Placebo	227	4.0

Abbreviations: AE, adverse event.

The results of the direct comparison were not statistically significant (Table 75).

Table 75: Discontinuation due to AEs at 52±4 weeks: Results from direct comparison of reslizumab 3.0 mg/kg versus placebo

	Difference between means, reslizumab versus placebo (95% CI)
Fixed-effects model	0.70 (0.33; 1.5)
Random-effects model	0.70 (0.33; 1.5)
P-value of the Cochran test	0.46
I^2	0%

Abbreviations: AE, adverse event; CI, confidence interval.
An OR <1 indicates that reslizumab is better than placebo. Statistical significance is reached when the 95% CI excludes 1. I^2 is based on the Q statistic from the Cochran test and is a measure of heterogeneity.

4.9.2.11 Serious adverse events at 16±4 weeks

The inputs used in the direct comparison of reslizumab versus placebo are shown in Table 76.

Table 76: SAEs at 16±4 weeks: Reslizumab 3.0 mg/kg versus placebo direct comparison inputs

Study and follow-up period	Treatment arm	N	% of patients who experienced SAEs
Castro, 2011 (Res-5-0010) (15 weeks)	Reslizumab	53	3.80
	Placebo	53	1.89
Study 3081 (16 weeks)	Reslizumab	103	6.8
	Placebo	105	3.8
Study 3084 (16 weeks)	Reslizumab	395	6.3
	Placebo	97	10.3

Abbreviations: SAE, serious adverse event.

The results of the direct comparison were not statistically significant (Table 77).

Table 77: SAEs at 16±4 weeks: Results from direct comparison of reslizumab 3.0 mg/kg versus placebo

	Difference between means, reslizumab versus placebo (95% CI)
Fixed-effects model	0.82 (0.43; 1.55)
Random-effects model	0.82 (0.43; 1.55)
P-value of the Cochran test	0.28

	Difference between means, reslizumab versus placebo (95% CI)
I^2	22%

Abbreviations: SAE, serious adverse event; CI, confidence interval.
An OR <1 indicates that reslizumab is better than placebo. Statistical significance is reached when the 95% CI excludes 1. I^2 is based on the Q statistic from the Cochran test and is a measure of heterogeneity.

4.9.2.12 Serious adverse events at 52±4 weeks

The inputs used in the direct comparison of reslizumab versus placebo are shown in Table 78.

Table 78: SAEs at 52±4 weeks: Reslizumab versus placebo direct comparison inputs

Study and follow-up period	Treatment arm	N	% of patients who experienced SAEs
Study 3082 (52 weeks)	Reslizumab	243	10.0
	Placebo	241	14.0
Study 3083 (52 weeks)	Reslizumab	230	8.0
	Placebo	227	10.0

Abbreviations: SAE, serious adverse event.

The results of the direct comparison were not statistically significant (Table 79).

Table 79: SAEs at 52±4 weeks: Results from direct comparison of reslizumab versus placebo

	Difference between means, reslizumab versus placebo (95% CI)
Fixed-effects model	0.71 (0.47; 1.08)
Random-effects model	0.71 (0.47; 1.08)
P-value of the Cochran test	0.76
I^2	0%

Abbreviations: SAE, serious adverse event; CI, confidence interval.
An OR <1 indicates that reslizumab is better than placebo. Statistical significance is reached when the 95% CI excludes 1. I^2 is based on the Q statistic from the Cochran test and is a measure of heterogeneity.

4.9.3 *Conclusion*

In summary, the meta-analyses of outcomes from the reslizumab trials showed significantly greater improvements in FEV_1 at 16 and 52 weeks, ACQ score at 16 weeks, and AQLQ score at 16 and 52 weeks, with reslizumab versus placebo. The rates of clinically significant asthma exacerbations were significantly lower with reslizumab versus placebo over the course of the trials. No significant treatment differences in the numbers of patients hospitalised due to exacerbations were identified, although the numbers of these events were low. There were no significant differences between the reslizumab and placebo arms in the proportions of patients discontinuing due to AEs or experiencing serious adverse events (SAEs) during the trials.

4.10 *Indirect and mixed treatment comparisons*

As described in Section 4.1, an SLR was conducted to identify data from published studies on the efficacy and safety of reslizumab versus omalizumab in adult patients with severe persistent allergic (IgE-mediated) asthma. Studies identified through this SLR were used to perform an indirect treatment comparison of reslizumab with omalizumab (see technical report (95)). Results for outcomes from this analysis (exacerbations and ACQ) were used when estimating transition probabilities in the omalizumab arm of the cost-effectiveness analysis (see Section 5.3.2).

4.11 *Non-randomised and non-controlled evidence*

The only study of relevance to the current submission is Study 3085, an open-label, long-term safety extension of studies 3081, 3082 and 3083. This trial is summarised in Section 4.12.2.

4.12 *Adverse reactions*

Safety evidence provided by the pivotal Phase III studies C38072/3082, C38072/3083 and C38072/3081 is presented below. The methodology and efficacy data for these studies are described in Section 4.3 and Section 4.7, respectively.

4.12.1 *Studies reported in section 4.2*

4.12.1.1 C38072/3082

An overview of adverse reactions reported in C38072/3082 is presented in Table 80. The overall pattern of AEs by frequency, severity and relationship to study drug was similar between the reslizumab and placebo treatment groups. AEs with a frequency of at least 5% in either treatment group are summarised in Table 81 by preferred term.

Only treatment-emergent adverse events (TEAEs), defined as AEs that occurred on or after the first dose of study drug, are included in the summary tables. The endpoint for AEs was the last post-baseline observation, which included the 90-day follow-up visit. Approximately 20 patients in each treatment group did not enter the open-label extension study C38072/3085 and attended the 90-day follow-up visit; these patients could have therefore contributed AE data for events that occurred after the Week 52 or early withdrawal visit.

Table 80: Summary of AEs in C38072/3082 – SAS

AEs, n (%)	Reslizumab 3.0 mg/kg N=245	Placebo N=243
Any AE[†]	197 (80)	206 (85)
Mild	68 (28)	41 (17)
Moderate	107 (44)	133 (55)
Severe	22 (9)	32 (13)
Treatment-related AEs[‡]	36 (15)	36 (15)
Mild	24 (10)	23 (9)
Moderate	9 (4)	13 (5)
Severe	3 (1)	0
SAEs	24 (10)	34 (14)
Deaths	0	1 (<1)
AE leading to discontinuation	4 (2)	8 (3)

Abbreviations: AE, adverse event; CI, confidence interval; SAE, serious adverse event; SAS, safety analysis set. [†]Treatment-emergent AEs, which included all non-serious and serious AEs that began or worsened after starting treatment with study drug. [‡]As assessed by the investigator.

Table 81: AEs occurring in ≥5% of patients in either treatment group – SAS

AEs, n (%)	Reslizumab 3.0 mg/kg N=245	Placebo N=243
Asthma	97 (40)	127 (52)
Upper respiratory tract infection	39 (16)	32 (13)
Nasopharyngitis	28 (11)	33 (14)
Sinusitis	21 (9)	29 (12)
Headache	19 (8)	30 (12)
Influenza	18 (7)	23 (9)
Bronchitis	13 (5)	24 (10)
Back pain	13 (5)	13 (5)
Urinary tract infection	13 (5)	11 (5)
Oropharyngeal pain	13 (5)	8 (3)
Rhinitis allergic	13 (5)	6 (2)
Nausea	12 (5)	10 (4)
Cough	11 (4)	13 (5)
Pharyngitis	10 (4)	13 (5)
Dyspnea	10 (4)	12 (5)
Fatigue	6 (2)	11 (5)
Dizziness	5 (2)	13 (5)

Abbreviations: AE, adverse event; CI, confidence interval; SAS, safety analysis set.

4.12.1.2 C38072/3083

An overview of adverse reactions reported in C38072/3083 is presented in Table 82. The overall pattern of AEs by frequency, severity and relationship to study drug was similar between the reslizumab and placebo treatment groups. AEs with a frequency of at least 5% in either treatment group are summarised in Table 83 by preferred term.

Only TEAEs, defined as AEs that occurred on or after the first dose of study drug, are included in the summary tables. The endpoint for AEs was the last post-baseline observation, which included the 90-day follow-up visit. A total of 88 patients (41 reslizumab and 47 placebo) did not enter the open-label extension study C38072/3085 and attended the 90-day follow-up visit; these patients could have therefore contributed AE data for events that occurred after the Week 52 or early withdrawal visit.

Table 82: Summary of AEs in C38072/3083 – SAS

AEs, n (%)	Reslizumab 3.0 mg/kg N=232	Placebo N=232
Any AE[†]	177 (76)	201 (87)
Mild	67 (29)	36 (16)
Moderate	98 (42)	140 (60)
Severe	12 (5)	25 (11)
Treatment-related AEs[‡]	34 (15)	27 (12)
Mild	22 (9)	14 (6)
Moderate	11 (5)	13 (6)
Severe	1 (<1)	0
SAEs	18 (8)	23 (10)
Deaths	0	0
AE leading to discontinuation	8 (3)	9 (4)

Abbreviations: AE, adverse event; CI, confidence interval; SAE, serious adverse event; SAS, safety analysis set. [†]Treatment-emergent AEs, which included all non-serious and serious AEs that began or worsened after starting treatment with study drug. [‡]As assessed by the investigator.

Table 83: AEs occurring in ≥5% of patients in either treatment group – SAS

AEs, n (%)	Reslizumab 3.0 mg/kg N=232	Placebo N=232
Asthma	67 (29)	118 (51)
Nasopharyngitis	45 (19)	56 (24)
Headache	33 (14)	17 (7)
Back pain	12 (5)	8 (3)
Upper respiratory tract infection	8 (3)	16 (7)

Abbreviations: AE, adverse event; CI, confidence interval; SAS, safety analysis set.

4.12.1.3 C38072/3081

An overview of adverse reactions reported in C38072/3081 is presented in Table 84. The overall pattern of AEs by frequency, severity and relationship to study drug was generally similar between the reslizumab and placebo treatment groups. AEs with a frequency of at least 5% in either treatment group are summarised in Table 85 by preferred term.

Only TEAEs, defined as AEs that occurred on or after the first dose of study drug, are included in the summary tables. Because AEs were assessed at the 90-day follow-up visit for approximately 10 patients in each treatment group, the data presented in the tables below also includes any events that occurred in these patients after the Week 16 or early withdrawal visit and during the follow-up period.

Table 84: Summary of AEs in C38072/3081 – SAS

AEs, n (%)	Reslizumab 0.3 mg/kg N=103	Reslizumab 3.0 mg/kg N=103	Placebo N=105
Any AE[†]	59 (57)	61 (59)	66 (63)
Severe	2 (2)	7 (7)	4 (4)
Treatment-related AEs[‡]	6 (6)	12 (12)	8 (8)
Severe	0	1	1 (<1)
SAEs	0	4 (4)	1 (<1)
Deaths	0	0	0
AE leading to discontinuation	1 (<1)	6 (6)	10 (10)

Abbreviations: AE, adverse event; CI, confidence interval; SAE, serious adverse event; SAS, safety analysis set. [†]Treatment-emergent AEs, which included all non-serious and serious AEs that began or worsened after starting treatment with study drug. [‡]As assessed by the investigator.

Table 85: AEs occurring in ≥5% of patients in any treatment group – SAS

AEs, n (%)	Reslizumab 0.3 mg/kg N=103	Reslizumab 3.0 mg/kg N=103	Placebo N=105
Asthma exacerbation	6 (6)	16 (16)	20 (19)
Upper respiratory tract infection	3 (3)	5 (5)	3 (3)
Nasopharyngitis	6 (6)	6 (6)	4 (4)
Headache	8 (8)	11 (11)	6 (6)
Bronchitis	5 (5)	2 (2)	5 (5)

Abbreviations: AE, adverse event; CI, confidence interval; SAS, safety analysis set.

4.12.2 *Additional studies*

A separate search for safety studies was not performed. Instead, a broad systematic literature search to identify both clinical and safety studies was conducted (see Section 4.1).

In addition to the RCTs reported in Section 4.12.1, safety evidence for reslizumab is provided by Study 3085, an open-label, long-term safety extension of studies 3081, 3082 and 3083 (Table 86). Study 3085 is summarised below.

Table 86: List of additional safety studies

Trial no. (acronym)	Population	Intervention	Comparator	Primary study ref(s)	Refs identified but not used further	Is study excluded from further discussion?
Phase III studies						
C38072/ 3085 (Study 3085)	Patients aged 12–75 years who completed one of the previous Teva-sponsored double-blind studies (C38072/3081, C38072/3082 and C38072/3083)	Reslizumab 3.0 mg/kg	NA. C38072/3085 was an open-label, long-term safety extension of the three previous studies	Clinical study report (114)	–	No

Abbreviations: NA, not applicable.

4.12.2.1 Summary of methodology of Study 3085

Table 87: Design and methodology of C38072/3085

Study objective	**Primary objective** To obtain additional safety data for reslizumab at a dose of 3.0 mg/kg every 4 weeks, relative to baseline, for up to 24 months in adolescent and adult patients with moderate to severe asthma and elevated blood eosinophils. **Secondary objectives** To evaluate the long-term efficacy of reslizumab as assessed by lung function, SABA use, ASUI score, ACQ score and AQLQ score.
Trial design	Phase III, multicentre, open-label extension of previous Teva-sponsored studies (C38072/3081, C38072/3082 and C38072/3083)
Method of randomisation and blinding	Not applicable
Key inclusion criteria	• Patients aged 12–75 years† with previous diagnosis of asthma • Completed treatment in a previous Teva-sponsored study (C38072/3081, C38072/3082, or C38072/3083) or have received at least 2 doses of study treatment in Study C38072/3081 • Willing and able to comply with the study
Key exclusion criteria	• Clinically meaningful comorbidity that would interfere with the study or compromise patient safety • Confounding underlying lung disorder • Current smoker • Any aggravating, inadequately-controlled medical factors • Current infection or disease that may preclude assessment of asthma • Any change in concomitant medications from baseline of the double-blind study was to be evaluated at screening/baseline for exclusion from the open-label study
Settings and locations	201 centres in 30 countries (Argentina, Australia, Belgium, Brazil, Canada, Chile, Colombia, Czech Republic, Denmark, France, Germany, Greece, Hungary, Israel, Malaysia, Mexico, New Zealand, Peru, Philippines, Poland, Romania, Russia, Slovakia, South Africa, South Korea, Sweden, Taiwan, Thailand, Ukraine, USA)
Duration of study	The study was conducted from June 2011 to January 2014 (termination date). The study was terminated due to enrolment that substantially exceeded the original planned sample size and the sponsor's conclusion that the primary study objective would have been substantially met at that time. The decision to terminate the study was not due to any new or emerging safety concerns. • The screening/baseline visit for C38072/3085 was the last visit of each of the three previous studies • Treatment period: Up to 24 months • Patients returned for a follow-up assessment 90 (±7) days after the end-of-treatment visit
Trial drugs	Reslizumab 3.0 mg/kg (N=1052), administered by intravenous infusion once every 4 weeks for up to 24 months
Prior and concomitant medications	Baseline asthma medications such as ICS, LABAs, leukotriene antagonists, 5-lipoxygenase inhibitors and cromolyn sodium were permitted during the study. Doses could be adjusted by the investigator based on best clinical practice. New medications that either treated asthma or could have an impact on asthma signs and symptoms could be initiated as long as they were not experimental or

	part of an ongoing clinical study. Prohibited medications were methotrexate, cyclosporin, interferon-α, anti-TNF monoclonal antibody, anti-hIL-5 antibody, omalizumab (Xolair)/ anti-IgE monoclonal antibody, and all other investigational drugs. Patients were to refrain from using SABAs for 6 hours, and LABAs for 12 hours, prior to any study visit.
Primary outcome	Safety as assessed by: • AEs throughout the study • Clinical laboratory tests at Weeks 4, 8, 24 and every 24 weeks thereafter • Physical examinations, vital signs and concomitant medication usage every 4 weeks throughout the study
Secondary outcomes	• Lung function tests (FEV_1, % predicted FEV_1, FVC and $FEF_{25–75\%}$) • ASUI score • ACQ score • AQLQ score • SABA use AQLQ was assessed every 24 weeks; all other secondary outcomes were assessed every 4 weeks for 16 weeks, at 24 weeks, and every 12 weeks thereafter
Pre-planned subgroups	No subgroup analyses were planned or conducted.

Abbreviations: ACQ, Asthma Control Questionnaire; AE, adverse event; AQLQ, Asthma Quality of Life Questionnaire; ASUI, Asthma Symptom Utility Index; FEV_1, forced expiratory volume in one second; $FEV_{25–75\%}$, forced expiratory flow at 25–75% forced vital capacity; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; SABA, short-acting beta-agonist.
†Patients aged 12–17 years of age were excluded from participating in Korea, India and Argentina; patients aged 66–75 years were excluded from participating in Korea and India.

4.12.2.2 Statistical analysis and definition of study groups in Study 3085

Table 88: Summary of statistical analysis in C38072/3085

Populations analysed	• Enrolled patients: All patients who were enrolled, regardless of whether or not they received any study drug • SAS: All patients who received ≥1 dose of reslizumab
Hypothesis	The clinical objective of C38072/3085 was to obtain additional safety data for reslizumab at a dose of 3.0 mg/kg every 4 weeks in adolescent and adult patients with asthma and elevated blood eosinophils.
Statistical information	**Analysis of the primary outcome** Safety analyses were based on the SAS and are summarised descriptively **Analysis of secondary outcomes** All efficacy analyses were performed on the SAS. Efficacy outcomes are presented by double-blind treatment group from the previous trials (reslizumab and placebo). All analyses are descriptive; no inferential statistics were planned or conducted.
Sample size and power calculations	The sample size was not based on power considerations; it was determined by the number of patients rolled over from the previous Phase III, double-blind, placebo-controlled studies of reslizumab (C38072/3081, C38072/3082 and C38072/3083).
Data management, patient withdrawals	Summary statistics are provided for observed data and missing data were not estimated. LOCF was applied in endpoint summaries.

Abbreviations: LOCF, last observation carried forward; SAS, safety analysis set.

4.12.2.3 Participant flow in Study 3085

Patient disposition

Patient disposition in C38072/3085 is presented in [redacted]36. A total of 1052 patients were enrolled in the study and [redacted] (>[redacted]%) received at least one dose of reslizumab and were evaluated for safety. Nearly [redacted] ([redacted] [redacted]%]) of the patients received reslizumab for the first time in C38072/3085, having received placebo in the preceding studies. A total of [redacted] ([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]

[redacted]36[redacted]

Baseline demographics and disease-specific characteristics

Patient demographics at entry into the open-label study were well balanced between the reslizumab-experienced and reslizumab-naïve groups ([redacted]89). Baseline disease-specific characteristics are presented in [redacted]90; as expected, lung function, patient-

reported measures of asthma control (ACQ, AQLQ, ASUI and beta-agonist use) and blood eosinophil count were better on average in patients who had received reslizumab in the preceding double-blind trials, compared with those previously treated with placebo.

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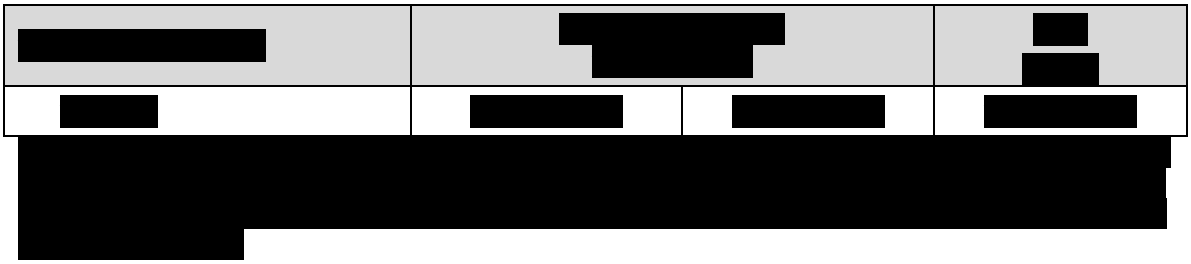

4.12.2.4 Quality assessment of additional safety studies

A quality assessment of Study 3085 is provided in Appendix 4.

4.12.2.5 Results of Study 3085

Primary outcome: Safety as assessed by AEs, clinical laboratory tests, physical examinations, vital signs and concomitant medication usage

Adverse events

A summary of the AEs reported in C38072/3085 is presented in Table 91. Events that occurred on or after the first dose of reslizumab up to the last post-baseline evaluation in the open-label study, including the 90-day follow-up period, are included. Ongoing AEs from the preceding trials were re-reported and included in the listings, but not the summaries. One ongoing AE from a previous study that worsened during treatment in the current open-label extension was updated and included in the summary of AEs.

More newly-exposed patients reported AEs compared with those previously treated with reslizumab (75% vs 67%). The majority of AEs were mild or moderate in severity; a total of 78 (7%) patients had severe AEs during the study period. With the exception of asthma, for which severe AEs occurred in 3% of patients, all severe AEs occurred in <1% of the total study population.

SAEs occurred in 78 (7%) of patients during the study. These events were most frequently reported in the respiratory, thoracic and mediastinal disorders system organ class (SOC) (25 [2%] patients), followed by the infection and infestations SOC (14 [1%] patients) and the neoplasms, benign, malignant and unspecified SOC (12 [<1%] patients). Except for asthma, SAEs were generally single-patient events. There was no clear difference between the previous double-blind treatment groups with respect to the frequency and type of SAEs reported.

There were three deaths during the study, two in the reslizumab-experienced group (one patient with haemoptysis, aspiration pneumonia, nervous system disorder and cardio-respiratory arrest, and one patient with a cardiac arrest) and one in the reslizumab-naïve group (anal cancer). These events were not considered to be related to the study drug.

Table 91: Summary of AEs in C38072/3085 – SAS

AEs, n (%)	Previous double-blind treatment group		Total N=1051
	Reslizumab 3.0 mg/kg N=571	Placebo N=480	
Any AE[†]	385 (67)	359 (75)	744 (71)
Mild	142 (25)	115 (24)	257 (24)
Moderate	196 (34)	213 (44)	409 (39)
Severe	47 (8)	31 (6)	78 (7)
AEs up to follow-up period	367 (64)	344 (72)	711 (68)
AEs in the follow-up period	82 (14)	78 (16)	160 (15)
Treatment-related AEs[‡]	41 (7)	49 (10)	90 (9)
Mild	19 (3)	27 (6)	46 (4)
Moderate	19 (3)	18 (4)	37 (4)
Severe	3 (<1)	4 (<1)	7 (<1)
SAEs	45 (8)	33 (7)	78 (7)
Deaths	2 (<1)	1 (<1)	3 (<1)
AE leading to discontinuation	12 (2)	6 (1)	18 (2)

Abbreviations: AE, adverse event; SAE, serious adverse event; SAS, safety analysis set.
[†]Treatment-emergent AEs, which included all non-serious and serious AEs that began or worsened after treatment with study drug. [‡]As assessed by the investigator.

The AE profile was similar between reslizumab-experienced and reslizumab-naïve patients during the study overall, and during both the treatment and follow-up periods. AEs with a frequency of at least 5% in either treatment group are summarised in Table 92 by preferred term; the most commonly-reported events overall were asthma (304 [29%] patients), nasopharyngitis (150 [14%] patients) and upper respiratory tract infection (108 [10%] patients).

Table 92: AEs occurring in ≥5% of patients in either treatment group – SAS

AEs, n (%)	Previous double-blind treatment group		Total N=1051
	Reslizumab 3.0 mg/kg N=571	Placebo N=480	
Asthma	159 (28)	145 (30)	304 (29)
Nasopharyngitis	81 (14)	69 (14)	150 (14)
Upper respiratory tract infection	57 (10)	51 (11)	108 (10)
Sinusitis	43 (8)	35 (7)	78 (7)
Headache	39 (7)	34 (7)	73 (7)
Bronchitis	29 (5)	33 (7)	62 (6)
Rhinitis allergic	31 (5)	19 (4)	50 (5)
Urinary tract infection	28 (5)	16 (3)	44 (4)

Abbreviations: AE, adverse event; SAS, safety analysis set.

Clinical laboratory evaluation

The results of clinical laboratory tests are summarised below:

- **Serum chemistry:** Mean values for serum chemistry parameters at baseline were similar in reslizumab-experienced and reslizumab-naïve patients. Changes from baseline during the treatment period were generally small, with no evidence of a treatment effect. Shifts in individual patient values from the normal range at baseline to outside the normal range during the treatment period generally occurred with similar frequency in both groups; no clinically relevant patterns were observed.
- **Haematology:** With the exception of eosinophil count and the resulting effect on total white blood cell (WBC) count, haematology cell counts and differentials were generally balanced between the previous double-blind treatment groups at baseline. Other than eosinophil count, there were no meaningful trends in change from baseline for any parameters, and no meaningful differences between previous treatment groups in the proportion of patients with shifts from the normal range at baseline to outside the normal range during the treatment period.
- **Urinalysis:** Mean urinary pH and specific gravity were similar between the previous double-blind treatment groups at baseline and there were no clinically meaningful trends in mean change from baseline during the study. There were no shifts in urinary pH from the normal range at baseline to outside the normal range during the treatment period; such shifts in specific gravity values occurred at a low frequency (generally ≤2%), and with a similar pattern in both groups.

Physical examination

As expected for a population with moderate to severe asthma, a notable proportion of patients in the reslizumab-experienced and reslizumab-naïve groups at baseline had abnormal examinations of head, eyes, ears, nose and throat (HEENT) (11% and 14%, respectively) and chest and lungs (15% and 22%, respectively). For each of the remaining physical examination categories, <10% of patients in each group had abnormal baseline findings. This pattern remained unchanged throughout the study. No clinically meaningful changes in height and weight parameters were observed during the study.

Shifts from baseline normal physical examination findings to abnormal post-baseline findings were uncommon and there were no clinically meaningful differences between the reslizumab-experienced and reslizumab-naïve groups.

Vital signs

Vital signs were similar across treatment groups at baseline and no clinically significant trends in change from baseline were observed during the treatment period. Other than a high incidence of low body temperature among adults (21% in both the reslizumab-experienced and reslizumab-naïve groups), the proportion of patients with potentially clinically significant values was low and similar between groups. Low body temperature was not considered to be meaningful; rather, it was likely due to variations in measurement technique and an overly stringent lower limit threshold.

Secondary outcomes: Efficacy variables

The primary objective of C38072/3085 was to evaluate the long-term safety of reslizumab. However, efficacy outcomes were also assessed as an indication of maintenance of effect. The results of secondary efficacy analyses are presented in *** 93 and summarised below:

- Baseline lung function was better in the reslizumab-experienced group, compared with the reslizumab-naïve group, as indicated by the higher mean FEV_1, % predicted FEV_1, FVC and $FEF_{25–75\%}$ values. Patients in the reslizumab-experienced group maintained their baseline FEV_1, % predicted FEV_1, FVC and $FEF_{25–75\%}$ throughout the treatment period, while improvements in all four outcomes were seen in patients newly exposed to reslizumab; these changes were apparent by the Week 4 visit and were consistent with the expected treatment effect observed in the previous placebo-controlled studies.
- Mean ASUI (a measure of asthma symptoms and side effects) and mean ACQ (a measure of asthma control) scores were [redacted] ([redacted] and [redacted], respectively) in the reslizumab-experienced group than the reslizumab-naïve group at baseline. Reslizumab-experienced patients [redacted] their baseline scores throughout the study, while [redacted] in both outcomes were observed in newly-exposed patients. These changes were apparent by Week [redacted] and were [redacted] with the treatment effect observed in the preceding studies.
- QoL as assessed by AQLQ score was [redacted] ([redacted]) in the reslizumab-experienced group than the reslizumab-naïve group at baseline. Reslizumab-experienced patients [redacted] their baseline AQLQ score throughout the study, while an [redacted] was observed in newly-exposed patients; this was apparent at Week [redacted] (the first assessment visit for this measure) and was [redacted] with the treatment effect observed in the preceding studies.
- Mean daily SABA use was [redacted] in the reslizumab-experienced group versus the reslizumab-naïve group at baseline. SABA use was [redacted] during the study in reslizumab-experienced patients, with [redacted] observed for newly-exposed patients.
- Mean blood eosinophil counts were [redacted] in the reslizumab-experienced group versus the reslizumab-naïve group at baseline. Reslizumab-experienced patients [redacted] their eosinophil level throughout the treatment period, while a [redacted] was observed in newly-exposed patients by Week [redacted] Eosinophil counts had [redacted] groups by the 90-day follow-up visit.

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4.12.3 *Safety overview*

4.12.3.1 Pooled AE data (Cohort 3)

During the application for EU marketing authorisation, data from the reslizumab clinical trials was integrated into cohorts for the evaluation of safety evidence. The cohort most relevant to the current NICE submission is Cohort 3, which included patients from the Phase II trial Res-5-0010, the pivotal Phase III trials 3081, 3082 and 3083 (for which AE data are summarised in Section 4.12.1), and the supportive Phase III trial 3084 (115, 116). This cohort contains the most robust set of placebo-controlled data available for the analysis of the reslizumab 3.0 mg/kg dose every 4 weeks in asthma patients.

In Cohort 3, 1870 patients were randomized and 1861 patients received at least one dose of study drug (SAS); 1463 (79%) of these 1861 patients had eosinophil counts ≥400 cells/μL at screening or baseline. A total of 1131 patients were treated with reslizumab (1028 with reslizumab 3.0 mg/kg and 103 with reslizumab 0.3 mg/kg) and 730 patients were treated with placebo. Of the 1028 patients treated with reslizumab 3.0 mg/kg, 438 (43%) were treated for ≥6 months (equating to 7 infusions) and 389 (38%) were treated for ≥12 months (equating to 13 infusions).

The overall pattern of AEs by frequency, severity and relationship to study drug was similar between the reslizumab 3.0 mg/kg and placebo groups (Table 94).

Table 94: Overview of AEs for Cohort 3

	Number (%) of patients	
	Reslizumab 3.0 mg/kg N=1028	**Placebo N=730**
Patients with ≥1 AE	**690 (67)**	**589 (81)**
Mild	252 (25)	144 (20)
Moderate	368 (36)	369 (51)
Severe	70 (7)	76 (10)
Patients with ≥1 treatment-related AE	**122 (12)**	**95 (13)**
Mild	77 (7)	53 (7)
Moderate	38 (4)	41 (6)
Severe	7 (<1)	1 (<1)
Patients who withdrew from a clinical study due to an AE	48 (5)	40 (5)
Deaths	0	1 (<1)
Patients with ≥1 SAE	65 (6)	66 (9)
Patients with ≥1 treatment-related SAE	5 (<1)	1 (<1)

Abbreviations: AE, adverse event; SAE, serious adverse event.

The incidence of all common AEs (≥2%) for any SOC was similar or lower for reslizumab than placebo with the exception oropharyngeal pain which was slightly higher in the reslizumab group than the placebo group. No AE by preferred term was reported to

occur with a frequency >1 percentage point higher with reslizumab compared with the corresponding placebo frequency. The most commonly reported AEs in the reslizumab 3.0 mg/kg treatment group were asthma (22.6%), nasopharyngitis (10.0%) and upper respiratory tract infection (9.3%) (Table 95).

Table 95: AEs occurring in ≥2% of patients in the reslizumab 3.0 mg/kg group – Cohort 3

	Number (%) of patients	
	Reslizumab 3.0 mg/kg N=1028	**Placebo N=730**
Asthma	232 (22.6)	289 (39.6)
Nasopharyngitis	103 (10.0)	103 (14.1)
Upper respiratory tract infection	96 (9.3)	69 (9.5)
Headache	78 (7.6)	62 (8.5)
Sinusitis	57 (5.5)	51 (7.0)
Bronchitis	34 (3.3)	52 (7.1)
Urinary tract infection	34 (3.3)	24 (3.3)
Back pain	33 (3.2)	25 (3.4)
Influenza	33 (3.2)	37 (5.1)
Rhinitis allergic	28 (2.7)	22 (3.0)
Oropharyngeal pain	27 (2.6)	16 (2.2)
Pharyngitis	23 (2.2)	25 (3.4)
Cough	22 (2.1)	23 (3.2)
Dyspnoea	22 (2.1)	20 (2.7)

Abbreviations: AE, adverse event.

4.12.3.2 AEs of special interest in Cohort 3

AE data from the clinical studies, as well as the known safety profile for biologics, were used to identify AEs of special interest. Infusion reactions, administration site reactions, hypersensitivity/anaphylaxis, malignancies, infections, and musculoskeletal/creatine phosphokinase (CPK) abnormalities were designated as AEs of special interest based on potential effects of the anti-IL-5 mechanism of action and on individual study results. Overall, a review of data related to these events did not raise any new safety concerns; a summary is provided below.

Infusion reactions and administration site reactions

In Cohort 3, AEs associated with the infusion were assessed as follows:

- AEs occurring during or within 24 hours were reported in 30% (306/1028) of patients receiving reslizumab 3.0 mg/kg compared with 39% (282/730) of patients receiving placebo. The most frequently reported event occurring within 24 hours of the infusion was asthma (6% and 14% in the reslizumab 3.0 mg/kg and placebo treatment groups, respectively).

- There were no meaningful differences between the reslizumab 3.0 mg/kg and placebo groups in the overall incidence of AEs under the high-level group term of Procedural-Related Injuries and Complications (<1% in both groups). No AEs under the high-level term of Transfusion-Related Complications were reported.
- Administration Site Reactions occurred at the same frequency (2%) in the reslizumab 3.0 mg/kg and placebo treatment groups. None of the administration site reactions/events were severe, serious, or resulted in discontinuation.

In conclusion, infusion reactions and administration site reactions were expected and consistent with the IV route of administration. The rates of these reactions were similar between patients treated with placebo and reslizumab.

Hypersensitivity and anaphylaxis

Anaphylaxis is a known risk of biologic treatments. Searches of the safety data were performed for the Standardized MedDRA Queries anaphylaxis and angioedema (broad and narrow):

- In Cohort 3, the incidence of broad anaphylaxis events as well as broad and narrow angioedema events was higher in placebo-treated patients compared with patients treated with reslizumab. In contrast, a narrow anaphylaxis search revealed five relevant cases in the reslizumab group (<1%) and no cases in the placebo group.
- Two cases were not temporally linked to reslizumab infusion, were associated with pre-known food allergy and immunotherapy, and did not result in discontinuation of reslizumab. Three of the five cases of anaphylaxis (with symptoms of skin or mucosal involvement, dyspnea, wheezing, gastrointestinal symptoms, and chills) had a temporal link to infusion, were assessed as related to reslizumab, and resulted in discontinuation of reslizumab treatment. Two cases occurred on the second infusion, and one case occurred on the eleventh infusion.
- All cases were observed in ADA-negative female patients (two of whom had medical history of hypersensitivity/anaphylaxis) and no reaction involving hemodynamic or pulmonary compromise. They fully resolved after standard treatment at the study centre. Due to the overlap in signs and symptoms, it was not possible to distinguish between anaphylaxis, other hypersensitivity reactions, or an infusion reaction in all cases.

Malignancies

- In the reslizumab clinical trials, cases of malignancy were reported with a slight numerical imbalance between those arising in the reslizumab-treated groups compared with control groups. Eight (<1%) of the 1861 patients in the SAS for Cohort 3 had at least 1 malignant neoplasm reported by the investigator (6 of 1028 [<1%] patients in the reslizumab 3.0 mg/kg treatment group and 2 of 730 [<1%] patients in the placebo group).
- There was no malignancy in the reslizumab 0.3 mg/kg treatment group. This treatment group was small (n=103) and had an observation period of only 16 weeks.
- All malignancies, except skin SCC in a patient previously diagnosed with prostate cancer, were diagnosed within 6 months of initiation of treatment, suggesting that

these were pre-existing conditions.

Infections

- In Cohort 3, 45% percent of patients had at least 1 AE reported under the SOC of Infections and Infestations and the high-level group term of Microbiology and Serology Investigation. A higher incidence of events indicative of infection was reported in the placebo treatment group (53%, event rate 162.56 per 100 patient-years) compared with the reslizumab 3.0 mg/kg treatment group (41%, event rate 130.86 per 100 patient-years). The specific types of infections and incidence were generally similar across treatment groups.

Musculoskeletal system

- Myalgia occurred at a similar frequency in reslizumab 3.0 mg/kg-treated patients (0.97%) and placebo-treated patients (0.55%) in Cohort 3. There was a slightly higher incidence of AEs reported under the Musculoskeletal and Connective Tissue Disorders SOC within the 24 hours of infusions in the reslizumab group compared with placebo group (23 [2.2%] and 11 [1.5%] patients, respectively). In general, these events were mild, transient, and did not recur with continuing reslizumab treatment. There was 1 discontinuation each for myalgia in the placebo and reslizumab 3.0 mg/kg groups. There were no related reports of myopathy, myositis, or rhabdomyolysis.
- Searches of the safety data for a broad-based group of terms associated with muscle disorders showed a similar incidence in the reslizumab 3.0 mg/kg (83 [8.1%] patients) and placebo (75 [7.8%] patients) groups. Pharmacokinetics/pharmacodynamics analyses suggest a relationship between reslizumab exposure and musculoskeletal AEs; however, this was driven by 5 overweight/obese female patients with high reslizumab concentrations and non-specific complaints of back pain and foot pain.

4.12.3.3 Study 3085

In the long-term safety extension study 3085, exposure to study drug was similar between patients previously treated with reslizumab and those previously treated with placebo. The mean duration of exposure to study drug was 356.4 days for reslizumab-experienced patients and 335.4 days for the reslizumab-naïve group. A complete infusion was defined as receiving at least 75% of the planned dose by the patient; over half of the patients received ≥11 complete infusions in this open-label study (54% and 56% in the reslizumab-naïve and reslizumab-experienced groups, respectively). As reported in Section 4.12.2, the overall AE profile was similar between the reslizumab-experienced and reslizumab-naïve groups during the study.

4.12.3.4 AEs of special interest in Study 3085

No anaphylactic reactions were reported in Study 3085.

Fifteen (1.4%) patients were diagnosed with malignancies during Study 3085. Patients with previous malignancies were not excluded; five of the patients with malignancies reported during this study had previous medical history of malignancies and two had a recurrence of their previous malignancy. The most frequent sites of malignancy were

breast, melanoma (including in situ), and basal cell carcinoma of the skin, reported by three patients each. These sites are common and expected for this patient population in a study of this duration.

4.12.3.5 Conclusion

In conclusion, the overall pattern of AEs in the reslizumab clinical trials was consistent with what would be expected in a moderate to severe, predominantly adult asthma population. No new safety concerns were reported with longer-term reslizumab treatment in the extension study, compared with the double-blind studies.

4.13 *Interpretation of clinical effectiveness and safety evidence*

4.13.1 *Principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology*

4.13.1.1 Summary of efficacy evidence

Efficacy evidence to support reslizumab for the treatment of patients with asthma and elevated blood eosinophils who are inadequately controlled with medium to high dose ICS comes from four Phase III, placebo-controlled RCTs (the Phase III BREATH programme):

- Studies 3082, 3083 and 3081 provide the core efficacy evidence. The 3082 and 3083 trials had an identical design and evaluated reslizumab 3.0 mg/kg administered every 4 weeks over 52 weeks. 3081 evaluated reslizumab 0.3 mg/kg and 3.0 mg/kg administered every 4 weeks over 16 weeks.
- Study 3084 provides supporting evidence for the current submission. This trial assessed the efficacy of reslizumab 3.0 mg/kg, given every 4 weeks for 16 weeks, in relation to baseline blood eosinophil levels in patients with moderate to severe asthma. The subpopulation of patients with a baseline eosinophil level ≥400 cells/μL, the cut-off for the definition of eosinophilic asthma in the reslizumab Phase III confirmatory trials, is relevant for the indication being appraised.

Asthma exacerbations

Frequency of CAEs was the primary endpoint in Study 3082 and Study 3083. Both trials met the primary endpoint, with reslizumab leading to a significantly greater reduction in the frequency of adjudicated CAEs during the 52-week treatment period compared with placebo ($p<0.0001$ in both trials). The majority of patients with a CAE experienced at least one CAE that required systemic (primarily oral) corticosteroids. All sensitivity analyses of the primary outcome demonstrated a significantly lower CAE frequency with reslizumab versus placebo, supporting the results of the primary analysis.

Lung function

Lung function as assessed by FEV_1 was the primary endpoint in Study 3081 and Study 3084, and a secondary endpoint in Studies 3082 and 3083. All four trials showed significant improvements from baseline with reslizumab compared with placebo:

- In Studies 3082 and 3083, significant improvements in FEV_1 were observed with reslizumab versus placebo over 16 weeks of treatment ($p<0.0001$ and $p=0.0037$, respectively). Improvements were evident by the first assessment visit (Week 4) and were sustained throughout the 52-week treatment period (nominal $p<0.0001$ and nominal $p=0.0057$, respectively, over 52 weeks).
- In Study 3081, both reslizumab doses led to a significantly greater improvement in FEV_1 over 16 weeks, compared with placebo. The treatment effect was greater for the 3.0 mg/kg dose ($p=0.0018$) than the 0.3 mg/kg dose ($p=0.0237$), indicating that the higher dose provides the most robust efficacy in this patient population. Sensitivity analyses of the primary outcome supported the results of the primary analysis.

- In Study 3084, there was a significant improvement in FEV_1 at Week 16 (p=0.0436) in patients with a baseline eosinophil level ≥400/µL. No significant treatment effect was observed at Week 16 in patients with baseline eosinophils <400/µL, or in the overall population at Week 16 or over 16 weeks.

Asthma control and symptoms

In Studies 3082 and 3083 there were significant improvements from baseline in patient-reported measures of asthma control (ACQ score) and asthma symptoms (ASUI score) with reslizumab versus placebo over 16 weeks of treatment. Improvements in these outcomes were evident by the first assessment visit (Week 4) and were sustained throughout the 52-week treatment period.

- In 3082 and 3083, ACQ was significantly improved (decreased) with reslizumab versus placebo over 16 weeks (p=0.0001 and p=0.0032, respectively) and over 52 weeks (nominal p=0.0002 and nominal p=0.0003, respectively). The proportions of patients achieving at least a 0.5-point improvement in ACQ score were greater with reslizumab than with placebo at almost all timepoints. ASUI was significantly improved with reslizumab versus placebo over 16 weeks and over 52 weeks in both trials (3082: p<0.0001 over 16 weeks and nominal p<0.0001 over 52 weeks; 3083: p=0.0037 over 16 weeks and nominal p=0.0011 over 52 weeks).
- Reslizumab treatment led to significant improvements versus placebo in ACQ and ASUI over 16 weeks in Study 3081; the degree of improvement was generally greater in patients treated with the 3.0 mg/kg dose (p=0.0014 and p=0.0160, respectively) than those given 0.3 mg/kg (p=0.0329 and p=0.0094, respectively).
- In 3084, the effect of reslizumab treatment on improved asthma control tended to increase slightly with increasing baseline blood eosinophil level. The proportion of patients in the overall population who achieved at least a 0.5-point improvement in ACQ score was numerically higher with reslizumab than placebo by Week 4; this treatment effect increased throughout the study, with significant differences seen at Weeks 12 and 16.

Quality of life

In 3082 and 3083, significant improvements from baseline in patient-reported QoL, as assessed by AQLQ score, were observed with reslizumab versus placebo over 16 weeks of treatment (p=0.0143 and p=0.0259, respectively); improvements were evident by the first assessment visit (Week 16) and were sustained throughout the 52-week treatment period (nominal p=0.0004 and nominal p=0.0052, respectively, over 52 weeks). A significant improvement in QoL was reported with reslizumab 3.0 mg/kg versus placebo in 3081 (p=0.0241); a numerical improvement versus placebo was seen for the reslizumab 0.3 mg/kg dose.

SABA use

Overall, reslizumab treatment resulted in less frequent SABA use over 16 weeks in the Phase III trials. The difference versus placebo was significant with both reslizumab doses Study 3081, and was numerical in Studies 3082 and 3083. In Study 3084, treatment with reslizumab resulted in a substantial reduction in SABA use at Week 16 for

patients with baseline eosinophils ≥400/μL, compared with placebo, although this result was not significant.

Blood eosinophil count

A significantly greater decrease in blood eosinophil levels was observed with reslizumab versus placebo in Studies 3082 and 3083, consistent with the mechanism of action of this IL-5 monoclonal antibody. Significantly greater reductions were also seen with both reslizumab doses in Study 3081, and in the overall reslizumab population (not stratified by baseline eosinophil level) in Study 3084.

Meta-analysis

Meta-analyses of outcomes from the reslizumab Phase II studies 3081, 3082, 3083 and 3084, and the Phase II study Res-5-0010 were conducted (Section 4.9). These analyses showed that there were significantly greater improvements in lung function at 16 and 52 weeks, asthma control at 16 weeks, and QoL at 16 and 52 weeks with reslizumab 3.0 mg/kg compared with placebo. The rates of clinically significant asthma exacerbations were significantly lower with reslizumab versus placebo over the course of the trials. No significant treatment differences in the numbers of patients hospitalised due to exacerbations were identified, although low numbers of these events were reported.

4.13.1.2 Summary of safety evidence

Reslizumab was generally well tolerated with a safety profile similar to that of placebo (summarised in Section 4.12.3). The most common AEs associated with reslizumab treatment in the RCTs included asthma, nasopharyngitis and upper respiratory tract infection. Across all trials the majority of TEAEs in patients treated with reslizumab were mild or moderate in severity. SAEs were uncommon; the incidence of SAEs in patients who received at least one dose of study drug was slightly lower in those treated with reslizumab 3.0 mg/kg (6%) compared with placebo (9%). One death occurred in the RCTs (placebo group in Study 3082); this was most likely due to accidental combined drug intoxication with fentanyl and diphenhydramine. Infusion reactions, administration site reactions, hypersensitivity/anaphylaxis, malignancies, infections, and musculoskeletal/CPK abnormalities were designated as AEs of special interest based on potential effects of the anti-IL-5 mechanism of action and on individual study results. Overall, a review of data related to these events did not raise any new safety concerns (Section 4.12.3.2).

Meta-analyses of safety data from the reslizumab Phase II and III RCTs showed that there were no significant differences between the reslizumab and placebo arms in the proportions of patients discontinuing due to AEs or experiencing SAEs during the trials (see Section 4.9.2).

The open-label, long-term safety extension Study 3085 (Section 4.12.2) was conducted to obtain additional safety data for reslizumab 3.0 mg/kg. The overall pattern of AEs in this trial was similar to the preceding double-blind studies and no new safety concerns were identified with continuous reslizumab treatment every 4 weeks for up to an additional 24 months.

4.13.2 *Strengths and limitations of the clinical evidence base for the technology*

4.13.2.1 Strengths of the evidence base

The Phase III RCTs (3081, 3082, 3083 and 3084) were multicentre, randomised, placebo-controlled studies to evaluate the efficacy and safety of reslizumab. In the pivotal trials 3082 and 3083, reslizumab 3.0 mg/kg was administered every 4 weeks for a period of up to 52 weeks. The RCTs were conducted in a large number of countries worldwide, including several in Europe. They were double-blind to minimise bias, and subjects were randomised using Interactive Response Technology (IRT).

The reslizumab trials successfully address the decision problem and are relevant to the final NICE scope. The study populations were representative of patients with asthma and elevated eosinophils who are inadequately controlled on medium to high dose ICS. Baseline demographics and disease-specific characteristics were generally similar across the trials and were well-balanced between the treatment groups in each trial. More female subjects than male subjects were enrolled in each trial, reflective of the gender imbalance in clinical practice (4, 22).

The endpoints in the RCTs were recognised, clinically-relevant outcomes and were in line with the NICE scope (see details in Section 4.3.3). The primary endpoint in studies 3082 and 3083 was the frequency of CAEs, and an adjudication committee was formed to ensure uniformity in determining whether investigator-determined CAEs met the required criteria. The primary endpoint in Study 3081 and the supportive Study 3084 was the change from baseline in lung function as measured by FEV_1.

The primary endpoint was met for reslizumab 3.0 mg/kg in studies 3082 and 3083, and for both reslizumab 3.0 mg/kg and 0.3 mg/kg in Study 3081. In Study 3084, which was designed to characterise the efficacy of reslizumab in relation to baseline blood eosinophil levels, the primary endpoint was met for patients with a baseline eosinophil level of ≥400 cells/μL (the subgroup relevant to the current submission). The robustness of the primary efficacy results was confirmed in multiple sensitivity analyses. As summarised in Section 4.13.1 above, meta-analyses of the data from the reslizumab RCTs supported the efficacy and safety findings of the individual trials.

4.13.2.2 Potential limitations of the evidence base

No UK-specific studies have been performed as part of the reslizumab Phase III clinical programme. However, as described above, the RCTs included patients at a large number of sites worldwide and were conducted in patients that can be considered as representative of the UK severe eosinophilic asthma population. The results of the trials are therefore generalisable for clinical practice in the UK.

The population defined in the final NICE scope is ‘adults with asthma with elevated blood eosinophils inadequately controlled by ICS’. However, it should be noted that studies 3081, 3082 and 3083 enrolled patients aged 12–75 and therefore also included adolescents. The mean age of patients in the three trials ranged from 44–47 years.

The use of blood eosinophil count rather than sputum eosinophil count as a marker of eosinophilic airway inflammation in the reslizumab Phase III trials could be regarded as a

limitation. However, as described in Section 3.1.2, while the measurement of eosinophils in induced sputum is a sensitive and reliable biomarker for identifying eosinophilic inflammation in asthma, it is not practical for use in large-scale clinical studies or for most community healthcare providers. Blood eosinophil counts are easier to obtain and several studies have shown them to correlate closely with sputum eosinophil levels (14, 42-44).

4.13.3 *End-of-life criteria*

Reslizumab is not considered an end-of-life treatment (Table 96).

Table 96: End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	No
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	No
The treatment is licensed or otherwise indicated for small patient populations	No

Abbreviations: NHS, National Health Service.

4.14 *Ongoing studies*

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.

5 Cost effectiveness

5.1 *Published cost-effectiveness studies*

5.1.1 *Identification of studies*

A SLR was conducted to identify economic models and studies reporting economic outcomes and data related to the treatment of asthma patients. The following databases were searched:

- MEDLINE (via PubMed) and MEDLINE (R) In-process (via PubMed)
- Embase
- EconLit

The search algorithms used in these databases were generated using the PICOS framework (Population, Intervention, Comparators, Outcomes, Study design) in line with the research question (Table 97). Search algorithms were tailored to identify studies published as of 04 April 2016.

Table 97: PICOS framework – cost-effectiveness, QoL and resource use SLRs

	Notes
Population	Adults with severe eosinophilic asthma
Interventions	Pharmacological interventions
Comparators	Pharmacological interventions
Outcomes	• Costs and resource use • Utilities • Modelled health states • Other economic outcomes • Patients utility scores and QoL data
Study type	• Health economic evaluations • Model-based cost-effectiveness models • Population-based studies

Abbreviations: QoL, quality of life; SLR, systematic literature review.

In addition to the above searches within key databases, 'grey' literature (i.e. material that can be referenced but is not typically published in peer-reviewed, database-indexed medical journals) was also searched for relevant meeting abstracts or posters. Proceedings for the following key conferences from the past three years (as available) were reviewed for relevant abstracts:

- ERS
- ATS
- BTS
- CHEST
- AAAAI

Search strategies were developed in line with the NICE Methods Guide and are provided in Appendix 5.

Records identified from the searches underwent two rounds of screening according to pre-specified inclusion and exclusion criteria (Table 98). In the first round, two independent investigators evaluated the title/abstracts of all unique records. In the second round, full-texts/publications of all records that met the inclusion criteria during the title/abstract screening were retrieved and reviewed by two independent investigators. None of the exclusion criteria and all of the protocol-specified inclusion criteria had to be met for a record to pass this level. During both rounds of the screening process, discrepancies were resolved through consensus by a third investigator.

Table 98: Eligibility criteria used in the search strategy for the cost-effectiveness and QoL SLRs

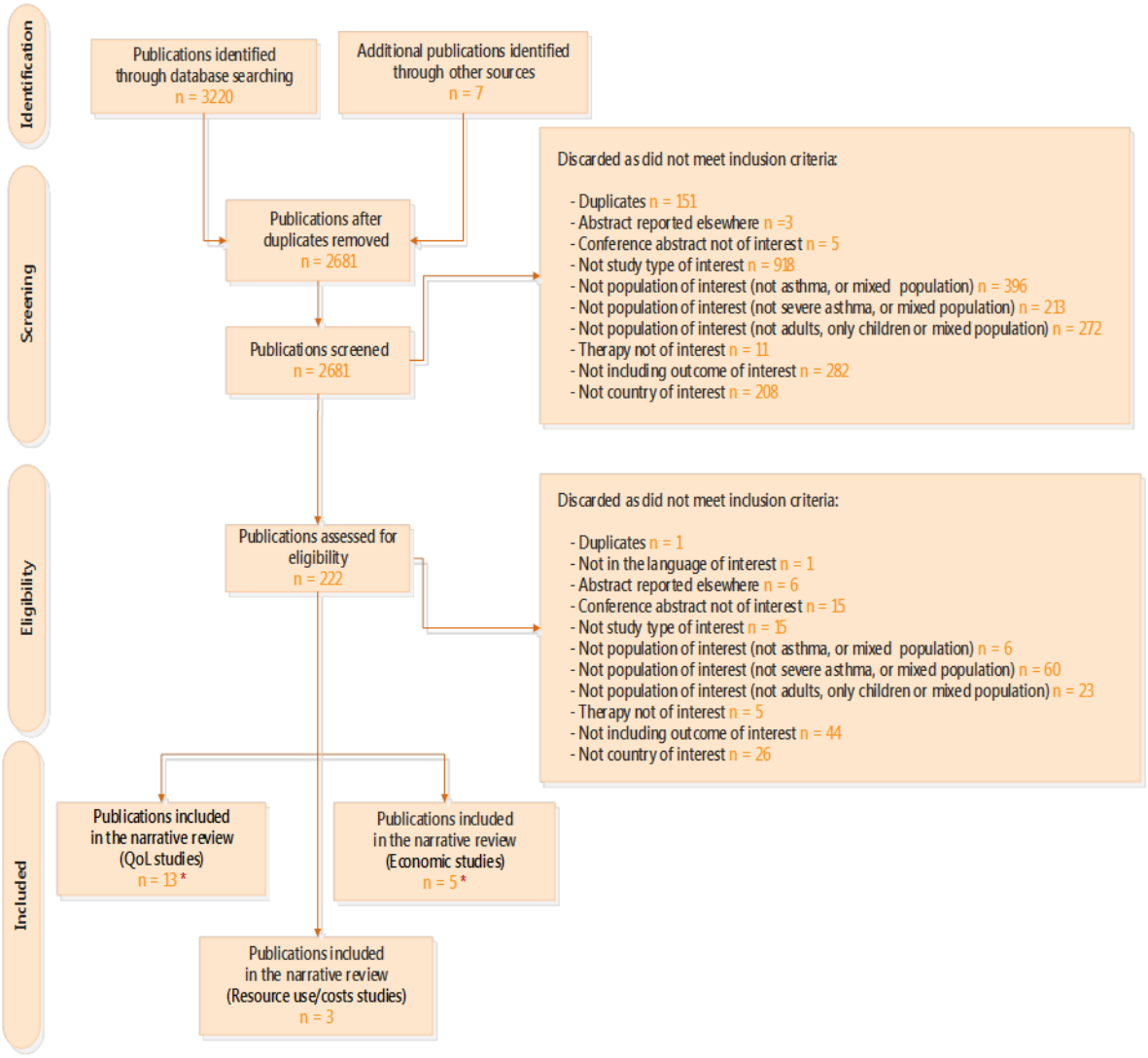
	Inclusion criteria	Exclusion criteria
Population	• Severe asthma • Adults	• Non-human • Not severe asthma • Not including adults
Intervention	Reslizumab (in addition to BSC)	
Comparators	All asthma therapies	
Outcomes	The outcome measures to be considered for the economic evaluation and quality of life 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 model • Population-based study	RCTs
Language restrictions	English	Any language other than English

Abbreviations: BSC, best standard of care; CE, cost-effectiveness; RCT, randomised controlled trial; QoL, quality of life.

Relevant data elements were extracted by one investigator and validated by a second independent investigator. All discrepancies were resolved in discussion with a third investigator. A number of control measures were put in place to ensure the quality and consistency of data extraction. These include pilot testing of the extraction form on several included studies, resolution of potential ambiguities and differences in the interpretation of findings, and written instructions on outcomes measures to be extracted from the full papers.

A global search strategy was run in order to identify key evidence in the cost-effectiveness, QoL, and costs and resource use SLRs. A total of 3,227 citations were identified, 3,220 through database searching and 7 through hand searches of other sources. After removal of duplicate papers, 2,681 publications were screened, of which 2,459 were excluded due to not meeting the inclusion criteria. 222 papers were reviewed in full, of which 201 were excluded. Five studies were included, two from the electronic database search (117, 118) and three additional references identified through a hand search of HTA and scientific conference websites (119-121). A schematic of the three SLRs is shown in Figure 37.

Figure 37: Schematic for the SLRs of cost-effectiveness, QoL and healthcare resource use evidence



5.1.2 *Description of identified studies*

The five relevant studies identified through the cost-effectiveness SLR are summarised in Table 99.

Table 99: Summary of included cost-effectiveness studies

Study	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Faria, 2014 (117) (Adapted analysis of Norman)	Markov model	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).	Omalizumab: 14.13 Standard of care: 13.66	Omalizumab: £60,406 Standard of care: £33,153	List price ICER: £83,822 PAS price ICER: £57,557
Faria,2013 (119)	Markov model	Patients with severe asthma	NR	NR	£32,398
Norman, 2013 (121)	Markov model	Adults and adolescents (greater than 12 years old) with severe uncontrolled asthma)	Omalizumab: 14.13 Standard of care: 13.66	Standard of care: £33,218 Omalizumab: £72,938	ICER: £83,222 Subgroup hospitalised for 12 months prior: £46,431 Subgroup maintenance OCS: £50,181
Willson, 2014 (118)	Markov model	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.	Tiotropium + usual care: 14.59 Usual care: 14.36	Tiotropium + usual care: £44,116 Usual care: £38,919	£21,906
Mepolizumab NICE technology appraisal (120)	Markov model	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	NR	NR	**Mepolizumab vs standard of care** Company submission: 1) Company proposed

		year or dependency on maintenance OCS			population: £19,526 2) ITT population: £31,659 3) Company proposed population excluding patients on maintenance OCS with <4 exacerbations: £15,394 NICE ERG analyses: 1) Company proposed population: £35,440 2) ITT population: £72,596 3) Company proposed population excluding patients on maintenance OCS with <4 exacerbations: £33,520 **Mepolizumab vs omalizumab and vs standard of care alone in the overlap ITT population** 1) Mepolizumab dominated 2) Standard of care: £105,455

Abbreviations: ACQ-7, asthma control questionnaire 7; ERG, Evidence Review Group; GINA, Global Initiative for Asthma; ICER, incremental cost-effectiveness ratio, ICS, inhaled corticosteroid; ITT, intent-to-treat; LABA, long-acting beta agonist; NR, not reported; OCS, oral corticosteroids; PAS, patient access scheme; QALY, quality-adjusted life year.

5.1.3 *Quality assessment of identified studies*

Quality assessments are provided in Appendix 6.

5.2 *De novo analysis*

5.2.1 *Patient population*

According to ERS/ATS guidelines (8) asthma can be subdivided into phenotypes in order to adapt treatment and management. Reslizumab is indicated as add-on therapy in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment. In line with the NICE scope and marketing authorisation, the reslizumab clinical trials evaluated the reslizumab treatment effect in severe eosinophilic asthma. The eosinophilic asthma designation covers two potential phenotypes:

- Purely eosinophilic asthma
- Eosinophilia linked to allergic asthma

The population considered for the base case analysis in the economic model was adult patients at GINA Steps 4 and 5 who had experienced at least three exacerbations in the preceding year. Other groups considered as part of scenario analyses were:

- Adult patients at GINA Step 4/5 who had experienced at least two exacerbations
- Adult patients at GINA Step 4/5 who had experienced at least four exacerbations

Although patients on chronic OCS are of interest because of a high unmet therapeutic need, the reslizumab pivotal trials did not allow patients to decrease their dose of OCS, in order to not confound the relative treatment effect of reslizumab as an add-on therapy to BSC versus BSC. As a result, sufficient evidence was not available to quantify the impact of treating patients with reslizumab on the use of corticosteroids, and this subgroup could not be investigated further.

5.2.2 *Model structure*

A lifetime Markov model was developed to compare the costs and outcomes of reslizumab add-on therapy with BSC alone (without reslizumab), and with omalizumab add-on therapy.

The model is comprised of six mutually exclusive health states (Figure 38), with the theoretical cohort able to transition between the ‘Controlled asthma’, ‘Uncontrolled asthma’, ‘Moderate exacerbation’, and ‘Severe exacerbation’ states. There are also two death states in the model, ‘Asthma-related mortality’ and ‘All-cause mortality’, both of which are absorbing. In this model it is assumed that a patient can only die from asthma-related causes having suffered a severe exacerbation, whereas patients are able to transition to all-cause mortality from any given health state. In the first cycle of the model, all patients are assumed to start in the ‘Uncontrolled asthma’ health state. The cohort then cycles through the model at discrete intervals of four weeks over a lifetime time horizon.

The controlled and uncontrolled asthma health states are defined based on the ACQ score. Patients are classed as having uncontrolled asthma if their ACQ score is ≥1.5, in line with the BTS/SIGN guideline (22).

Based on recommendations from clinical experts consulted during the development of the current model, the severity of exacerbations is defined according to the ERS/ATS guidelines (8).

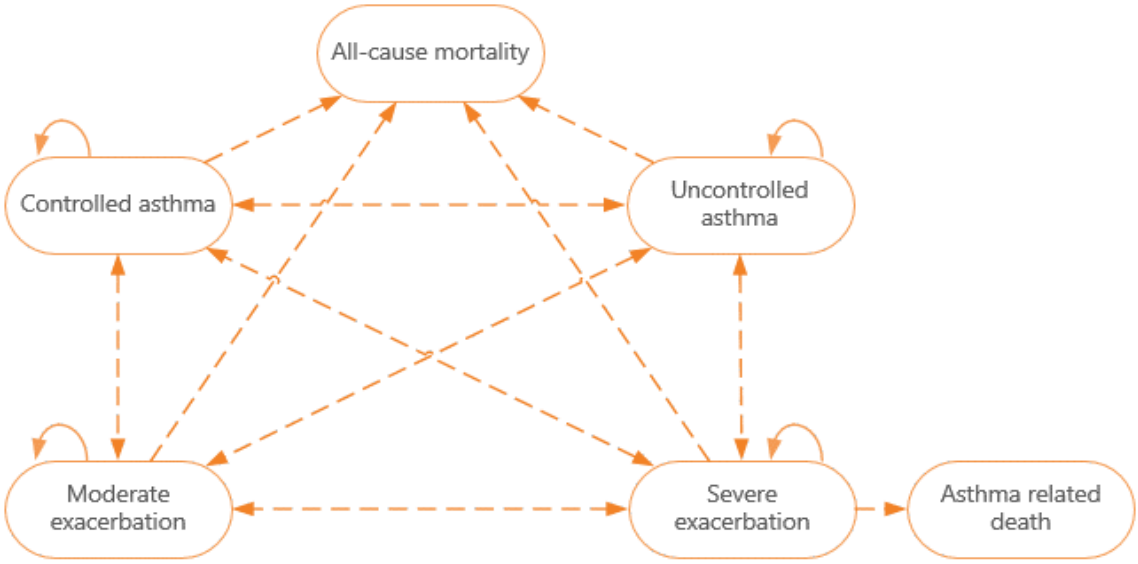
A moderate exacerbation is defined as an exacerbation associated with one or more of the following events:

- Deterioration in 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.

Figure 38: Model structure



In this model, both the omalizumab and reslizumab treatment arms are subject to a response rule. In line with the omalizumab SmPC (35), patients in the omalizumab arm are assessed for treatment response at 16 weeks into therapy. At 16 weeks after commencing omalizumab therapy patients should be assessed by their physician for treatment effectiveness before further injections are administered'.

As introduced in Section 3.3.1, treatment response for patients on reslizumab in the model was identified according to [redacted]

The reference point of [redacted] was selected for the model as indicative of early improvement because it represents the timepoint by which improvements in asthma impairment, as measured by [redacted] were expected to have plateaued in most

patients based on the results of the Phase 3 studies. The first [redacted] assessment was performed at [redacted] weeks, which allowed quality of life to be factored into the model. Patients would have received [redacted] doses of reslizumab 3mg/kg by 16 weeks.

The definitions of a responder or non-responder at 52 weeks are outlined in ***[redacted]100.

[redacted]100

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

[redacted]

[redacted] Other patients (responders and those with an undetermined response status) are assumed to continue treatment beyond 16 weeks.

Patients are assumed to be assessed every year (every 13 cycles) in line with the reslizumab SmPC, and it was assumed that patients who remain in the uncontrolled or exacerbation health states for one year will discontinue treatment. This assumption was presented to and validated by a panel of UK clinical experts during an advisory board. The same discontinuation rule was applied to omalizumab for consistency.

5.2.2.1 Key features of the de novo analysis

The key features of the economic analysis are presented in Table 101.

Table 101: Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	Lifetime (60 years)	Long enough to reflect all important differences in costs or outcomes between technologies. Reflective of clinical practice.
Were health effects measured in QALYs; if not, what was used?	Yes, QALYs were used	N/A
Discount of 3.5% for utilities and costs	Yes, although the value is user-modifiable in the model	N/A
Perspective (NHS/PSS)	NHS and PSS, 2015	N/A

Abbreviations: N/A, not applicable; NHS, National Health Service; PSS, Personal Social Services; QALY, quality-adjusted life year.

5.2.3 *Intervention technology and comparators*

The intervention therapy is reslizumab as add-on therapy to BSC. The comparators modelled are BSC without reslizumab, and omalizumab as add-on therapy to BSC (for patients with severe persistent allergic asthma with elevated blood eosinophils).

For reslizumab and BSC, the progression of disease was modelled based on the 3082 and 3083 pivotal trials.

For the comparison with omalizumab, limited data were available for the overlap population (i.e. patients with both an eosinophilic [IL-5-mediated] and allergic [IgE-mediated] asthma phenotype). It was therefore not possible to conduct a comparison in this restricted population via an NMA. The relative treatment effect was therefore estimated based on the total population enrolled in the omalizumab clinical trials which involved patients with lower levels of eosinophils. The underlying assumption of this analysis is that the relative treatment effect of omalizumab is similar in patients with both normal and elevated levels of eosinophils.

5.3 *Clinical parameters and variables*

5.3.1 *How are clinical data incorporated into the model?*

The cost-effectiveness model is set to a lifetime time horizon while the pivotal clinical trials (studies 3082 and 3083) were conducted over 52 weeks. As described in the following sections, the probabilities of death and death due to asthma were available by age and did not require extrapolation. Conditional probabilities of transitioning between asthma control, uncontrolled asthma and exacerbations were based on the 52-week clinical trial data.

5.3.2 *Transition probabilities*

5.3.2.1 BSC treatment arm

The transitions probabilities were computed using patient level data from the two pivotal reslizumab clinical trials (studies 3082 and 3083) (76, 77). The total pooled population

from these trials included 953 patients, of which 476 were treated with BSC. Analysis was limited to patients who were ≥18 years of age and classified as GINA Step 4/5 in the asthma treatment pathway and having experienced 2 exacerbations or more in the preceding year, giving a population of 159 in the BSC treatment arm. A total of 91 patients from the BSC arm had experienced three exacerbations or more in the preceding year, a sample size that was too limited to generate robust transition probabilities. Therefore the transition probabilities were estimated on patients having experienced two exacerbations or more, and the baseline risk of exacerbations was adjusted as described below.

A scenario analysis was run based on transition probabilities estimated on all adult patients (≥18 years) GINA Step 4/5 in the asthma treatment pathway, which corresponds to 372 patients randomised to the BSC treatment arm.

A patient's health state was identified at each study visit. This facilitated the tracking of health states over time, allowing the calculation of the transition probabilities between the three mutually exclusive health states, 'Controlled asthma', 'Uncontrolled asthma', and 'Exacerbation'. Patients were classified into the three health states at each visit using the following criteria:

- Controlled asthma: ACQ score <1.5
- Uncontrolled asthma: ACQ score ≥1.5
- Exacerbation (regardless of asthma control): If the patient suffered a moderate or a severe exacerbation since the last visit

Due to insufficient data, moderate and severe exacerbations were pooled for the computation of transition probabilities.

To delineate between moderate and severe exacerbations, the percentage of severe exacerbations (i.e. associated with the use of systemic corticosteroids) out of the total number of exacerbations reported in studies 3082 and 3083 were used: 76.3% of exacerbations experienced by patients in the reslizumab arm were severe; this percentage was estimated at 81.8% for the BSC arm. Adult patients in GINA Step 4 or 5 enrolled in the 3082 and 3083 trials had experienced an average of 1.99 exacerbations over the preceding year. Over the course of the trial, patients randomised to placebo had an average of 1.34 exacerbations per year, reflecting a potential placebo effect. Similar differences were reported in the different subpopulations of interest (Table 102).

Table 102: Mean annual rate of exacerbations in patients randomised to placebo (studies 3082 and 3083)

Subpopulation	N	Year prior to randomisation	Trial follow-up
Adults; GINA Step 4 and 5	**740**	**1.99**	**1.34**
Adults; GINA Step 4 and 5; ≥2 exacerbations in the preceding year	307	3.37	2.13
Adults; GINA Step 4 and 5, ≥3 exacerbations in the preceding year	158	4.67	2.73
Adults; GINA Step 4 and 5, ≥4 exacerbations in the preceding year	94	5.81	2.88

Abbreviations: GINA, Global Initiative for Asthma.

To reflect the rates of exacerbations expected to be observed in clinical practice, a multiplier was applied to the probabilities of transitioning to match the rate of exacerbations reported in the year preceding enrolment in the clinical trial. The same multiplier was applied to all transition probabilities of moving to the exacerbation health states (Table 103).

Table 103: Transition probabilities – BSC population – patients having experienced ≥3 exacerbations in the preceding year

		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

Abbreviations: BSC, best standard of care.
Values have been rounded for the purpose of presentation.

Two absorbing states were added to this set of probabilities in order to build the transition network. The origins of these two additional transitional probabilities are described below.

All-cause mortality:

- Transition probabilities were taken from National UK life tables (123) and adjusted for cycle length.

Asthma-related mortality:

- The transition from ‘Severe exacerbation’ to ‘Asthma-related mortality’ could not be estimated from the clinical trials as severe exacerbations are rare events: a total of 31 exacerbations across treatment arms were reported in the trial. The probability of this transition was therefore calculated using odds ratios from a study by Roberts et al (21), applied to the National UK life tables (123). The probability of asthma-related mortality was therefore dependent upon age.
- Roberts et al (21) describe trends in 30 day case-fatality following hospitalisation for asthma in adults in Scotland from 1981–2009. The odds ratios presented by the authors were calculated using a logistic regression model adjusted for age, sex, year, socioeconomic deprivation and comorbidities. The cost-effectiveness model uses the adjusted odds ratios presented in Table 104.
- Another publication (Watson et al (20)) also provides data on asthma-related mortality and was considered for use in the model. However, the study by Roberts et al was chosen as it stratifies patients into narrower age bands than those in Watson et al,

thus providing more accurate asthma mortality estimates.

Table 104: Logistic regression models for 30 day case-fatality after asthma admission taken from Roberts et al, 2013

	Unadjusted odds ratio	Lower 95% CI, upper 95% CI	Adjusted odds ratio	Lower 95% CI, upper 95% CI
Age group 18–24	1.0 (reference)		1.0 (reference)	
Age group 25–34	1.0	0.5, 1.8	1.1	0.6, 2.2
Age group 35–44	1.4	0.8, 2.5	1.4	0.7, 2.7
Age group 45–54	3.1	1.8, 5.2	2.4	1.3, 4.4
Age group 55–64	8.9	5.4, 14.6	6.3	3.6, 11.1
Age group 65+	19.6	12.1, 31.8	12.3	7.1, 21.3
Sex	0.8	0.71, 0.9	0.9	0.8, 1.0
Carstairs–Morris index of Socioeconomic deprivation				
1st quintile (least deprived)	1.0 (reference)		1.0 (reference)	
2nd quintile	1.3	0.2, 1.7	1.4	1.1, 1.9
3rd quintile	1.1	0.2, 1.4	1.3	1.0, 1.8
4th quintile	0.9	0.1, 1.2	1.1	0.8, 1.4
5th quintile (most deprived)	1.0	0.1, 1.2	1.1	0.9, 1.5
Emergency admission	0.9	0.7, 1.1	1.2	0.9, 1.6
Asthma hospitalisation in last 12 months	0.9	0.7, 1.0	0.9	0.8, 1.1
Comorbidity				
Diabetes	2.1	1.6, 2.6	1.1	0.8, 1.5
Cancer	5.2	4.1, 6.6	2.6	2.0, 3.5
Coronary heart disease	4.1	3.6, 4.7	1.6	1.4, 2.0
Essential hypertension	1.4	1.2, 1.8	0.8	0.6, 1.0
Cerebrovascular disease	3.8	2.9, 4.9	1.5	1.0, 2.1
Renal failure	5.9	4.3, 8.2	2.5	1.7, 3.9
Respiratory infections	1.7	1.5, 2.0	1.5	1.1, 1.8
Cor pulmonale	8.3	5.7, 12.3	1.9	1.1, 3.2
Respiratory failure	5.2	4.2, 6.6	4.0	3.0, 5.3

[a] The reference group consisted of men, aged 18–24 in deprivation quintile 1 (least deprived) in 1981, not an emergency admission and no comorbidities.

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 was estimated based on data provided by a clinical expert, who estimated the mean annual rate of exacerbation 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%).

5.3.2.2 Reslizumab treatment arm

Three different transition matrices were computed for the reslizumab treatment arm, according to the assumptions of the model:

- Transition probabilities from 0–16 weeks for the whole reslizumab-treated population
- Transition probabilities from 16–52 weeks, excluding patients identified as non-responders to treatment at week 16
- Transition probabilities after 52 weeks for responders to treatment

Assessment of response

As described in Section 5.2.2, assessment of response was made at 16 weeks based on an algorithm [redacted]

[redacted]

The distribution of the reslizumab-treated population, in terms of treatment response is presented in Table 105. The base case analysis assumes that early non-responders do not continue treatment beyond 16 weeks. Therefore, only early responders and patients with an indeterminate level of response continue treatment beyond 16 weeks in the model.

Table 105: Identification of non-response to reslizumab in patients with ≥2 exacerbations in the preceding year (studies 3082 and 3083)

	Responders	Non-responders	Indeterminate	Total
Percentage of total patients	78.3%	13.2%	8.5%	**100%**
Adult patients at GINA Step 4/5	81%	10%	9%	**100%**

0–16 weeks

The 0–16 week transition probabilities were computed using data from the reslizumab-treated population before assessment of response at 16 weeks. 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.

Table 106: Transition probabilities over 0–16 weeks for the reslizumab arm – population with ≥3 exacerbations in the preceding year

		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

16–52 weeks

The 16–52 week transition probabilities were computed using data from patients who were either identified as early responders to treatment or who had an undetermined response according to the algorithm, using data reported from Weeks 16–52 in the clinical trials. Similarly to the 0-16 weeks, the same multiplier as BSC was applied to all transition probabilities to the exacerbation health states. The results are presented in Table 107.

Table 107: Transition probabilities over 16–52 weeks for the reslizumab arm – population with ≥3 exacerbations in the preceding year

		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

Post-52 weeks

In the reslizumab treatment arm, patients who remain uncontrolled or experience moderate or severe exacerbations for 12 consecutive months (or 13 consecutive cycles) are assumed to discontinue treatment and transfer to the BSC arm. As data beyond 52 weeks of treatment with reslizumab were not available, transition probabilities beyond 52 weeks were based on data reported in responders according to the algorithm described above, which aims to identify responders at 52 weeks based on data available at 16 weeks.

The multiplicative factor for the number of exacerbations computed for the BSC population was also applied to all post-52 weeks transition probabilities purporting to the Exacerbation states for the 'responder to treatment' population for consistency purposes (i.e. in order to maintain the relative treatment effect of reslizumab versus BSC).

Table 108: Transition probabilities over 16–52 weeks in the reslizumab arm – population with ≥3 exacerbations in the preceding year

		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

5.3.2.3 Omalizumab treatment arm

In patients with allergic asthma, omalizumab is also a relevant comparator. As mentioned in Section 5.2.3, the comparison with omalizumab is subject to limitations as:

- IgE levels were collected in only one of the 3082 and 3083 trials and therefore the sample size of patients with high levels of IgE did not allow transition probabilities in this subgroup of patients to be estimated
- The omalizumab trials do not report results stratified by levels of eosinophils
- No omalizumab studies were identified to report the proportion of patients with asthma control.

As a result and based on the meta-analysis, the following approach was used:

0–16 weeks

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) (95). Given the lack of data related to ACQ stratified by category (i.e. controlled vs uncontrolled asthma), the conditional probabilities of moving to the controlled and uncontrolled states were assumed to be the same as for reslizumab, within patients not experiencing exacerbations. This approach was considered as conservative as the NMA estimated results in favour of reslizumab when considering double blind trials (mean ACQ score vs reslizumab at 16 weeks was estimated at –0.24 (95% CI –0.68; 0.19)) (95).

Table 109: Transition probabilities from 0 to 16 weeks - omalizumab – population with ≥3 exacerbations in the preceding year

		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

From 16 weeks

Patients in the omalizumab arm are assessed for treatment response at 16 weeks into therapy, in line with the omalizumab SmPC (35). At 16 weeks after commencing omalizumab therapy patients should be assessed by their physician for treatment effectiveness before further injections are administered. The proportion of responders to omalizumab according to this definition was retrieved from the omalizumab HTA: 56.5% (31). The relative rate of exacerbation in responders versus BSC: 0.373, was also retrieved from the same source. As for the transition probabilities from 0 to 16 weeks, the transition to controlled and uncontrolled asthma were based on the reslizumab transition probabilities due to a lack of data.

Table 110: Transition probabilities from 16 weeks - omalizumab – population with ≥3 exacerbations in the preceding year

		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 in the reslizumab treatment arm, omalizumab patients who remain uncontrolled or experience moderate or severe exacerbations for 12 consecutive months (or 13 consecutive cycles) are assumed to discontinue treatment and transfer to the BSC arm. As data beyond 52 weeks of treatment with omalizumab were not available, the same approach as for previous periods was taken.

The relative rate of exacerbation in responders versus BSC (0.373) was used to derive the probabilities of exacerbations post 52 weeks. As for the transition probabilities from 0 to 16 weeks, the transition to controlled and uncontrolled were based on the reslizumab transition probabilities due to a lack of data.

Table 111: Transition probabilities post 52 weeks in the omalizumab arm – population with ≥3 exacerbations in the preceding year

		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

5.3.2.4 Subgroup analysis

In addition to the population of interest for the base case analysis, several groups of interest were identified based on the unmet therapeutic need highlighted by clinical experts. In addition, an analysis was conducted to assess the cost-effectiveness of reslizumab in the global population of patients in GINA step 4/5 without restriction on the number of prior exacerbations.

For each of these subgroups, transition matrices were generated for both the BSC and reslizumab-treated populations according to the above methods, and calculating the

exacerbation multiplier so that the mean number of exacerbations predicted by the model for the BSC arm corresponds to the mean number of exacerbations experienced in the year preceding enrolment in the clinical trial for the subgroup of interest (see Table 102).

- 2 exacerbations or more in the preceding year (multiplier: 3.37 exacerbations/year)
- 4 exacerbations of more in the preceding year (multiplier: 5.81 exacerbations/year)
- Adult patients at GINA Step 4/5 (multiplier: 1.98 exacerbations/year)

5.3.3 *Clinical expert assessment of applicability of clinical parameters*

The following aspects of the modelling approach were presented to UK clinical experts. Their advice on the following was implemented:

- Model structure
- Discontinuation rules
- The most relevant target population for the base case analysis, identified based on the subgroup of patients who would benefit the most from treatment with reslizumab (i.e. patients with severe eosinophilic asthma and a history of exacerbations)
- Estimates of healthcare resource use
- Utility estimates by health state
- General approach to estimate transition probabilities based on the pivotal trials

5.4 *Measurement and valuation of health effects*

5.4.1 *Health-related quality-of-life data from clinical trials*

Patients provided data on asthma symptoms and functioning using the AQLQ in the clinical trials (75-78, 114). Patients were asked to recall their experiences during the last two weeks and to respond to each question on a seven point scale. The first five questions were activity questions and were patient-specific, meaning that each patient identified and scored five activities that were limited by their asthma. These five activities were identified at the first visit and their assessments were retained for comparison at all subsequent follow-up visits. AQLQ data was collected at Visits 2, 6, 10 and 15 (Weeks 0, 16, 32 and 52) in both Study 3082 and Study 3083 (76, 77).

All HRQoL data reported in the clinical trials were collected directly from the patients themselves. As the EuroQol 5-dimensions questionnaire (EQ-5D) is the preferred option for the measurement of HRQoL, AQLQ data was mapped onto EQ-5D using a mapping algorithm developed at the University of Sheffield. This algorithm allows preferences to be obtained from the condition-specific instrument (AQLQ) and then transformed into utilities (see Section 5.4.2) (124). Once utilities had been derived, QALYs could then be calculated. This method adheres to the guidelines stipulated in the NICE Reference Case (125).

5.4.2 *Mapping*

Mapping was used as part of a scenario analysis. For the base case, published estimates based on EQ-5D data were selected.

5.4.3 *Identification of health-related quality-of-life studies*

A SLR was conducted to identify studies from the published literature reporting HRQoL/utility data in severe asthma. Prior to the literature search, a pre-specified review protocol was developed, which detailed the electronic databases to be searched, the search strategy, and the inclusion and exclusion criteria to be used during screening.

Details of the four electronic databases searched are presented in Table 112; these databases include both published studies and conference abstracts. Only publications in English were considered.

Table 112: Electronic databases searched

Database	Service provider	Date of the search	Time period of the search
MEDLINE	PubMed	04/04/2016	2006 to present
MEDLINE-IN-PROCESS	PubMed	04/04/2016	2006 to present
EMBASE	OVID	04/04/2016	2006 to present
EconLit	OVID	04/04/2016	2006 to present

To supplement the electronic database searches, hand searches were conducted to identify relevant conference abstracts and posters presented in the past three years at key scientific conferences. The NICE website, reporting information on treatments for patients with severe asthma, was also searched. The retrieval of unpublished studies through the search of trial registries and conference proceedings is recommended in the NICE Guide to the methods of technology appraisal (125). Search terms used to identify relevant publications were related to the disease of interest (i.e. severe asthma). A list of the hand searches conducted is presented in Table 113.

Table 113: Hand searches conducted

Source type	Website used for hand searches
Conferences	• 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)
Regulatory documents	• National Institute for Health and Care Excellence (NICE), England

Records identified from the searches underwent two rounds of screening according to the pre-specified inclusion and exclusion criteria detailed in Table 98. In the first round, two independent investigators evaluated the title/abstracts of all records. In the second round, full-texts/publications of all records that met the inclusion criteria during the title/abstract screening were retrieved and reviewed by two independent investigators. During both rounds of the screening process, discrepancies were resolved by consensus through the use of a third investigator.

Relevant data elements were extracted by one investigator and validated by a second independent investigator. Once again, all disagreements were resolved in discussion with a third investigator. A number of control measures were put in place to ensure the quality and consistency of the data extraction. These include pilot testing of the extraction form on several included studies, resolution of potential ambiguities and differences in the interpretation of findings, and written instructions on outcome measures to be extracted from the full papers.

As described previously, a global search strategy was employed to identify key evidence related to the economic evaluation, HRQoL, and costs and resource use SLRs (Appendix 5). A total of 13 HRQoL/utility studies were included after several rounds of screening and review. For a full breakdown of all three SLRs, please refer to Section 5.1.1 and Figure 37.

5.4.4 *Description of identified studies*

The 13 relevant studies identified through the HRQoL/utility SLR are summarised in Table 99.

Table 114: Summary of HRQoL/utility studies identified through the SLR

Study, Country	Population	Recruit-ment	Interventions/ comparators	Sample size	Response rates	Adverse reactions	Elicitation method	Mapping	Health states	Utility score (95% CI)
Aburuz, 2007 UK (126)	Adult patients with difficult asthma	NR	NR	86	86/90	NR	i) AQLQ, ii) EQ-5D, iii) EQ-5D VAS	NR	Difficult asthma	i) 3.2 ii) 0.47 iii) 57.4
Cohen, 2013 Europe (127)	Patients suffering from severe allergic asthma	NR	NA	1248	1,248/ 132,805	NR	i) SF-12v2	NR	NR	i) 43.4 (MC) ii) 38.4 (PC)
Cummings, 2012 UK (128)	Adults with severe allergic asthma	NR	Omalizumab	9	NR	NR	i) AQLQ	NR	NR	i) 2.26
Lloyd, 2007 UK (129)	Patients with moderate to severe asthma (BTS Step 4 and 5)	NR	NA	112	NR	NR	i) Mini-AQLQ ii) EQ-5D iii) EQ-5D VAS iv) ASUI	NR	A) No exacerbation B) Exacerbation with OCS C) Hospitalisation	A) i) 4.72 ii) 0.89 iii) 76.21 iv) 0.75 B) i) 3.28 ii) 0.57 iii) 56.43 iv) 0.48 C) i) 2.28 ii) 0.33 iii) 49.00

Study, Country	Population	Recruit-ment	Interventions/ comparators	Sample size	Response rates	Adverse reactions	Elicitation method	Mapping	Health states	Utility score (95% CI)
										iv) 0.31
Menzella, 2012 Italy (130)	Patients with severe allergic asthma treated with omalizumab	NR	Omalizumab	11	NR	None	i) AQLQ	NR	NR	i) 2.8
D'Amato, 2014 NR (131)	Patients with severe asthma	NR	Nocturnal ventilation by continuous positive airway pressure (nCPAP)	10	10/11	NR	i) EQ-5D VAS	NR	NR	i) 53.5
Kupryś-Lipińska, 2014 Poland (132)	Patients with severe asthma treated with omalizumab	NR	Omalizumab withdrawal	11	NR	NR	i) AQLQ	NR	NR	i) 4.3
Novelli, 2013 Italy (133)	Patients with severe asthma	NR	NR	64	NR	NR	i) AQLQ	NR	A) Obese asthmatics B) Non-obese asthmatics	(A) i) 4.5 (B) i) 5.1
Thomson, 2013 UK (134)	Patients with severe refractory asthma recruited to the BTS Severe Asthma Registry	NR	NR	760	760/1,019	NR	i) AQLQ ii) EQ-5D iii) EQ-5D VAS iv) HAD	NR	A) Non-smoker B) Current smoker C) Ex-smoker	(A) i) 3.6 ii) 0.7 iii) 8 (AS), 6 (DS) (B) i) 3.0

Study, Country	Population	Recruit-ment	Interventions/ comparators	Sample size	Response rates	Adverse reactions	Elicitation method	Mapping	Health states	Utility score (95% CI)
										ii) 0.5 iii) 50 iv) 13 (AS), 10 (DS) (C) i) 3.3 ii) 0.5 iii) 50 iv) 9 (AS), 8 (DS)
Taille, 2014 France (135)	Patients with severe asthma	NR	Pulmonary rehabilitation	30	30/53	NR	i) SGRQ ii) HAD	NR	NR	i) 47 ii) 15
Mogal, 2014 UK (136)	Patients with severe allergic asthma	NR	Omalizumab	23	NR	NR	AQLQ	NR	NR	i) 1.9
Amelink, 2013) Netherlands (137)	Adult patients with a physician's diagnosis of asthma who had no major co-morbidities and were not pregnant	NR	NR	78	NR	NR	i) AQLQ	NR	Severe asthma	i) 4.8
de Carvalho-Pinto, 2012 Brazil (138)	Patients with severe asthma	NR	NA	74	74/128	NR	i) SF-36 ii) SGRQ	NR	Severe asthma	i) Physical function 34.9 Physical role 25.4

Study, Country	Population	Recruit-ment	Interventions/ comparators	Sample size	Response rates	Adverse reactions	Elicitation method	Mapping	Health states	Utility score (95% CI)
										Body pain 39.4 General health 40.5 Vitality 40.8 Social function 54.4 Emotional aspects 32.4 Mental health 50.1 ii) 67

Abbreviations: AQLQ, Asthma Quality of Life Questionnaire; AS, anxiety score; ASUI, Asthma Symptom Utility Index; BTS, British Thoracic Society; DS, depression score; EQ-5D, EuroQol-5D questionnaire; HAD, hospital anxiety and depression scale; HRQoL, health-related quality of life; MC, mental component; NA, not applicable; NR, not reported; OCS, oral corticosteroid; PC, Physical component; SF-12, Short Form-12 Questionnaire; SGRQ, St. George's Respiratory Questionnaire; VAS, visual analogue scale.

5.4.5 *Key differences*

HRQoL data was collected from the clinical trials using AQLQ. This data was then mapped to EQ-5D using an established algorithm (124), before being converted into utilities (see Section 5.4.2). Several of the papers captured in the QoL SLR also used AQLQ as a measure of QoL.

In the reslizumab Study 3082, AQLQ at baseline was reported for both the reslizumab and the placebo treatment arms (4.159 and 4.303, respectively) (76). The values reported in the other pivotal reslizumab trial, Study 3083, were similar to these (4.223 and 4.352, respectively) (77). In the literature, the overall baseline mean from the eight studies that reported AQLQ was 3.42 (126, 128, 130, 132-134, 136, 137); the three lowest AQLQ baseline scores were 1.9, 2.26, and 2.8, reported by Mogal et al (136), Cummings et al (128) and Menzella et al (130), respectively. All three of these papers focused on patients with severe allergic asthma treated with omalizumab. Given the difference in baseline means and the trend illustrated by the omalizumab studies, it is reasonable to assume that the difference in AQLQ score could be due to the definitions of severity used, and thus the populations analysed in the various studies.

5.4.6 *Adverse reactions*

In the four double-blind, randomised, placebo-controlled reslizumab trials (Studies 3081, 3082, 3083 and 3084), the most frequently reported AEs were worsening of asthma, upper respiratory tract infection, sinusitis, headache, nasopharyngitis, influenza or bronchitis. The overall pattern of AEs by frequency, severity and relationship to study drug was similar in the reslizumab and placebo/BSC groups, and thus AEs were not included in the model. This approach was also taken in a technology appraisal of omalizumab in severe persistent allergic asthma that was submitted to NICE.

5.4.7 *Health-related quality-of-life data used in cost-effectiveness analysis*

The model uses health state-specific utilities that are irrespective of treatment arm and were taken from Willson et al (118) and Lloyd et al (129). The analysis by Willson et al. estimates the cost-effectiveness of tiotropium add-on therapy in asthma patients who are uncontrolled despite treatment with ICS/LABA, from the perspective of the UK NHS. To collect HRQoL data the EQ-5D questionnaire was self-administered by patients at each visit in this study. The results provide EQ-5D scores for controlled (ACQ-6 score <1), partly-controlled (ACQ-6 score of 1–1.5), and uncontrolled (ACQ-6 score ≥1.5) asthma patients (118).

In the current model, the non-exacerbation health states were stratified into ‘Controlled asthma’ (ACQ score <1.5) and ‘Uncontrolled asthma’ (ACQ score ≥1.5). Given the differences in definition of these health states, it was first necessary to make adjustments to certain values before implementing them in the current model. The utility for ‘Uncontrolled asthma’ was taken directly from Willson et al. The ‘Controlled asthma’ health state utility was estimated as a weighted average of the controlled and partly controlled health state utilities from Willson et al, weighted by the proportion of time spent in asthma control (ACQ <1.5) and partly controlled asthma (ACQ between 1 and

1.5) in the 3082 and 3083 clinical trials: 49% of the assessments with an ACQ<1.5 were between 1 and 1.5.

In Willson et al (118) the utility associated with the non-severe exacerbation health state was estimated as the mid-point between uncontrolled asthma and severe exacerbation not leading to hospitalisation. The same approach was used for this model.

As in Willson et al, utilities associated with the two severe exacerbation health states (with and without hospitalisation) were taken from a prospective study by Lloyd et al conducted at four specialist asthma centres in the UK (129). Patients in this study had moderate to severe asthma defined (based on BTS/SIGN Step 4/5) as those treated with at least one high dose formulation of ICS plus any LABA, or any leukotriene-receptor antagonist. The findings provide EQ-5D scores collected within four weeks of a severe exacerbation managed with OCS (0.57) and asthma-related hospital admission (0.33).

A summary of the utility values used in the model is provided in Table 115. Utilities remained constant over time.

Table 115: Summary of utility values for cost-effectiveness analysis

Health state	Utility value	95% CI	Reference in submission	Justification
Uncontrolled asthma	0.728	0.707; 0.749	Willson et al, 2014 (118)	Health state definition used in the model is reconcilable with the definition used in this study
Controlled asthma	0.920	0.901; 0.943		Health state definition used in the model is reconcilable with the definition used in this study
Moderate exacerbation	0.57	0.549; 0.591	Lloyd et al, 2007 (129) Willson et al, 2014 (118)	Health state definition used in the model is reconcilable with the definition used in this study
Severe exacerbation	0.33	0.309; 0.351		Health state definition used in the model is reconcilable with the definition used in this study

Abbreviations: CI, confidence interval.

5.4.7.1 Clinical expert assessment of applicability of health state utility values

Utilities by health states were presented to and validated with UK clinical experts.

5.5 *Cost and healthcare resource use identification, measurement and valuation*

5.5.1 *Identification of studies*

A SLR was conducted to identify resource use and cost data related to the treatment of severe asthma patients. The following databases were searched:

- MEDLINE (via PubMed) and MEDLINE (R) In-process (via PubMed)
- Embase
- EconLit

The search algorithms used in these databases were generated using the PICOS framework (Population, Intervention, Comparators, Outcomes, Study design) in line with the research question (Table 97). Search algorithms were tailored to identify studies published as of 04 April 2016.

In addition to the above searches within key databases, 'grey' literature (i.e. material that can be referenced but is not typically published in peer-reviewed, database-indexed medical journals) was also searched for relevant meeting abstracts or posters. Proceedings for the following key conferences from the past three years (as available) were reviewed for relevant abstracts:

- ERS
- ATS
- BTS
- CHEST
- AAAAI

Search strategies were developed in line with the NICE Methods Guide (see Appendix 5).

Records identified from the searches underwent two rounds of screening according to the pre-specified inclusion/exclusion criteria. In the first round, two independent investigators evaluated the title/abstracts of all unique records. In the second round, full-texts/publications of all records that met the inclusion criteria during the title/abstract screening were retrieved and reviewed by two independent investigators. None of the exclusion criteria and all of the protocol-specified inclusion criteria had to be met for a record to have passed this level. During both rounds of the screening process, discrepancies were resolved through consensus by a third investigator.

Relevant data elements were extracted by one investigator and validated by a second independent investigator. All discrepancies were resolved in discussion with a third investigator. A number of control measures were put in place to ensure the quality and consistency of data extraction. These include pilot testing of the extraction form on several included studies, resolution of potential ambiguities and differences in the interpretation of findings, and written instructions on outcomes measures to be extracted from the full papers.

The search strategy for the costs and resource use SLR was part of a global search, along with the economic evaluation and HRQoL search strategies. A total of 3 costs and resource use studies were included after several rounds of screening and review. For a full breakdown of all three SLRs, please refer to Section 5.1.1 and Figure 37.

5.5.2 *Description of identified studies*

Resource use and cost data were extracted from three studies identified through the SLR (Table 116):

- Willson et al (118) provides data on medical resource use depending on the severity of asthma and exacerbations. This study assessed the cost-effectiveness of tiopropium as add-on therapy to BSC in asthma and was conducted in the UK setting.
- The study by O'Neill et al (139) is a registry analysis of 182 patients (61% male) with severe asthma as defined by GINA guidelines. 14% were current smokers and 11.2% were former smokers.
- The study by Thomson et al (134) is an observational study including 760 patients with severe asthma. Asthma severity was assessed using the ATS definition of severe refractory asthma. This study also reported relevant HRQoL data (see Section 5.4.4).

Table 116: Summary of included resource use studies

Study, Country	Currency	Year	Population	Total patient costs	Treatment costs	Direct costs/resource used	Indirect costs
Willson, 2014 (118) UK	GBP	2014	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	**Total weighted cost per week**: 1. Controlled asthma: £7.18 2. Partly-controlled asthma: £11.61 3. Uncontrolled asthma: £41.80 4. Non-severe exacerbation: £65.58 5. Severe exacerbation with hospitalisation: £83.50	Usual care (high dose LABA/ICS): £8.52 per week Tiotropium: £8.28 per week	**1. Inpatient resource use (cost per episode)** i) Asthma-related hospitalisations: £785.98 ii) Severe exacerbation-related hospitalisation: £1,524.28 iii) A&E visit only: £108.22 iv) A&E + hospitalisation: £1,691.49 v) Ambulance + hospitalisation: £1,763.93 vi) Ambulance + hospitalisation + A&E visit: £1,927.15 vii) Hospitalisation including ICU stay: £2,242.45 **2. Outpatient visits** i) Visit to GP: £43 per visit ii) Visit to Nurse: £13.69 per visit iii) Visit to Respiratory Specialist: £133.26 per visit iv) Visits from GP: £110.00 per visit v) Visit from nurse: £37.33 per visit **3. Laboratory test** Spirometry test: £28.20 Flu vaccine: £6.32 Desensitisation: £175.32 **4. Co-medication (cost per mg)** Prednisone: £0.067 Amoxicillin: £0.00015 Singulair: £0.17 Hydrocortisone IV: £0.011 Magnesium IV: £0.0033	NR
O,Neill, 2011 (139) UK	GBP	2006/ 2007	Difficult-to-control asthma was defined as persistent symptoms despite treatment at GINA Step 4/5.	**Per year (SE):** High estimate: £1,690.67 (101.37) Low estimate: £1,234.73 (121.23)	NR	**Per year (SE):** 1. Hospitalisation: £621.12 (71.25) 2. Out-patient visit: £185.46 (13.22)	NR

Thomson, 2013 (134) UK	GBP	2013	Patients with severe refractory asthma recruited to the BTS Severe Asthma Registry.	NR	NR	**Current smokers** 1. Hospitalisation in last year, median (range): 1 (0–12) 2. Unscheduled health care visit in last year, median (interquartile range): 6 (3–8) **Ex-smokers** 1. Hospitalisation in last year, median (range): 0 (0–14) 2. Unscheduled health care visit in last year, median (interquartile range): 4 (2–7) **Never smokers** 1. Hospitalisation in last year, median (range): 0 (0–13) 2. Unscheduled health care visit in last year, median (interquartile range): 4 (2–6)	NR

Abbreviations: A&E, accident and emergency; ACQ, Asthma Control Questionnaire; BTS, British Thoracic Society; GBP, Great British Pound; GINA, global Initiative for Asthma; GP, general practitioner; ICS, inhaled corticosteroid; ICU, intensive care unit; LABA, long-acting beta-agonist; NR, not reported; SE, standard error.

5.5.2.1 Appropriateness of NHS Ref costs/PbR tariffs

NHS reference costs cover a wide variety of conditions and are the most appropriate for costing purposes. Unit costs used in the model were sourced from NHS reference costs and PSSRU Unit costs of Health and Social Care 2015. These costs and the corresponding DRG codes and references are outlined in Table 117.

In some instances, unit costs were not reported for the specific resource to be costed. Therefore, some costs were derived though a weighted average of different sources, based on their reported occurrence. Examples of this methodology are indicated in the 'code' column of Table 117.

Table 117: NHS reference and PSSRU unit costs used in the model

Resource	Cost	Code	Source
Outpatient visits (from survey)	**Cost per visit**		
Visit to GP	£44.00	N/A	PSSRU 2015 (140)
Visit to nurse	£14.47	N/A	(15.5 minutes) PSSRU 2015 (140)
Home visit (from survey)	**Cost per visit**		
Visit from GP	£113.00	N/A	(11.4 minute consultation, 12 minute travel) PSSRU 2015, updated to 2016 using the health CPI (141)
Inpatients resource used (from the clinical trials)	**Cost per episode**		
Severe exacerbation-related hospitalisation	£1,629.97	DZ15M/N/P†	NHS reference costs schedule – 2014/2015 (142)
A&E visit only	£132.00	T01NA	
A&E visit + hospitalisation	£1,761.97	No specific unit cost - T01NA + DA15QR	
Ambulance + hospitalisation	£1,809.80	No specific unit costs – DZ15M/N/P† + ASS01 (ambulance)	
Ambulance + A&E + hospitalisation	£1,941.80	No specific unit cost - ASS01+ T01NA + DA15QR	
Hospitalisation including ICU stay	£2,567.62	No specific unit cost - DZ15M/N/P† + XC06Z (ICU stay)	

Abbreviations: A&E, Accident and Emergency; GP, general practitioner; ICU, intensive care unit; PSSRU, Personal Social Services Research Unit; N/A, not applicable; NHS, National Health Service.
†Average of the unit costs of three different codes that depend on severity of exacerbation.

5.5.2.2 *Clinical expert assessment of applicability of cost and healthcare resource use values*

Levels of healthcare resource use by health state, based on the publication by Willson et al (118), were presented and validated with clinical experts.

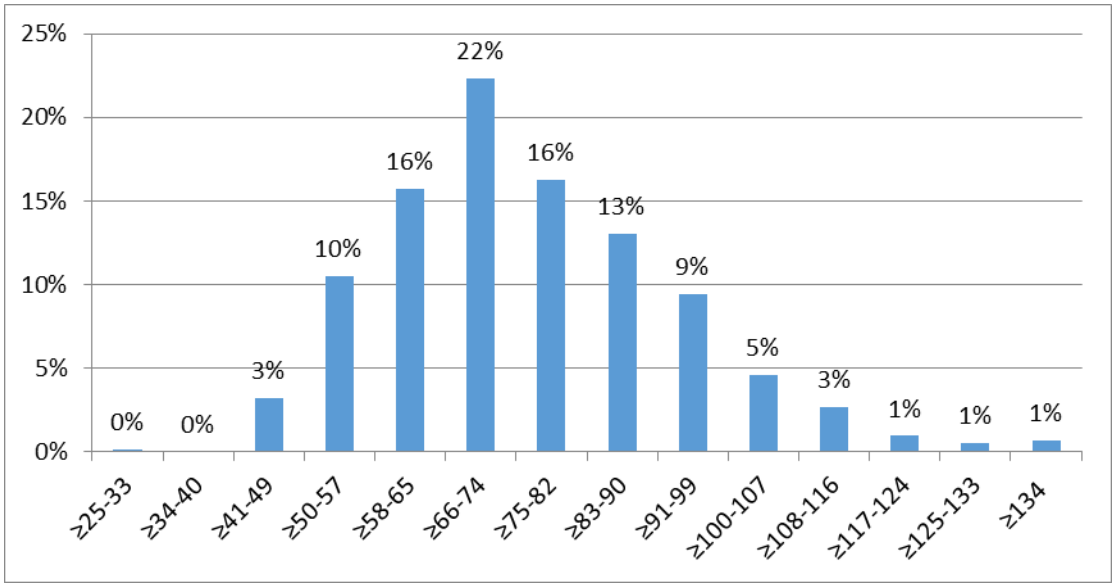
5.5.3 *Intervention and comparators' costs and resource use*

In the base case analysis, the mean cost of the reslizumab regimen is calculated considering drug wastage. This method takes into account the cost of all the vials opened. The wastage option is only relevant to reslizumab and not the comparators evaluated in the model.

Reslizumab is currently available through 10 mL vials which contain 100 mg of reslizumab each. However a 25 mg vial is currently under development and expected to be available between Q2 and Q3 2017. Given the fact that the 25 mg vial size will shortly be available, the base case analysis was based on this option, however the sole use of 100 mg vials was assessed in a scenario analysis and an analysis assuming vial sharing was also conducted.

Given the fact that all centres may not be able to share the vials between patients, the base case analysis assumes no vial sharing and the number of vials to be used was based on the distribution of patient weights, obtained from adult patients with a GINA Step of 4 to 5 enrolled in the 3082 and 3083 trials (see Figure 39). The mean weight was 75.2 kg.

Figure 39: Weight distribution in kg – adult patients at GINA Step 4/5 enrolled in the 3082 and 3083 trials



The costs associated with the use of reslizumab, omalizumab and BSC in the base case analysis are presented in Table 118.

Omalizumab is administered as a subcutaneous injection every 2-4 weeks (35). Dosing is determined by i) serum total IgE levels measured prior to treatment initiation and ii) the patient's body weight. To account for individual patient treatment schedules, UK cohort data taken from the INNOVATE trial (88) were used to create a dose distribution. From

this distribution the average omalizumab dosing schedule in the UK was calculated, which corresponds to a mean of 1.31 administrations per model cycle (of 28 days) (35).

Administration costs were calculated depending on the time needed by the nurse to administer biologics. Based on input from the reslizumab SmPC, and clinical expert opinion, it was assumed that a specialist nurse needs to be present for a total of 55 minutes during the administration process. Of those 55 minutes, 10 are spent preparing the treatment, 30 are spent administering the treatment to the patient, and the final 15 are used for monitoring purposes. The administration of omalizumab is assumed to only take 40 minutes. During this time the specialist nurse takes 10 minutes to prepare the treatment and administer to the patient. The remaining 30 minutes are used to monitor the patient after administration.

Table 118: Unit costs associated with the technology in the economic model

Treatment arm	Item	Cost	Source
Reslizumab	Technology cost: 100 mg/10 mL Technology cost: 25 mg/2.5 mL	[redacted] [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] [redacted] [redacted]	Teva UK Limited, PAS price
	Administration and monitoring cost/cycle (55 minutes specialist nurse)	£54.08	PSSRU, 2015 (140)
	Total	**Base case cycle cost: [redacted]**	
Omalizumab	Technology cost: 75 mg/mL	£128.07	BNF legacy, 18 March 2016
	Mean cost of treatment/cycle	£569.98	BNF legacy, 18 March 2016
	Administration and monitoring cost/cycle (40 minutes)	£39.33 1.31 per cycle £51.64/cycle	PSSRU, 2015 (140) INNOVATE (88) Omalizumab SmPC (31)
	Total	**Cycle cost: £621.62**	
BSC	Technology cost	£40.92	BNF legacy, 18 March 2016 Reslizumab studies 3082 and 3083
	Initiation cost	0	
	Mean cost of treatment/cycle	£40.92	
	Administration and monitoring cost/cycle	0	
	Total	**£40.92**	

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

5.5.4 *Health state costs and resource use*

Willson et al (118) used data from the PrimoTinA-asthma® clinical trial to estimate the resources used by each health state in their model for inpatients. To estimate the level of resource used for outpatients, a survey was conducted among healthcare practitioners in the UK. In total, 15 UK healthcare providers (5 GPs experienced in treating asthma patients, 5 asthma specialists and 5 respiratory nurses) were asked to evaluate the healthcare consumption by asthma patients being treated at GINA Step 4.

The model by Willson et al included seven different health states, whereas the current reslizumab model has five (Section 5.2.2). Several of these health states were found to be comparable. Consequently, the levels of resource use reported in Willson et al. were also used in the current model, with adjusted unit costs. For example, the resource use reported for 'Uncontrolled asthma', 'Non-severe exacerbation', 'Severe exacerbation – no hospitalisation', and 'Severe exacerbation – with hospitalisation' in Willson et al. were used as the health state costs for 'Uncontrolled asthma', 'Moderate exacerbation', 'Severe exacerbation – not leading to hospitalisation' and 'Severe exacerbation – not leading to hospitalisation' respectively (see Table 119). No medication costs were considered, as the costs of rescue medications and oral corticosteroids were assumed to be negligible compared to other medical costs and due to lack of robust data. Based on the definition of the model health states, no hospitalisations were accounted for in the controlled, uncontrolled, and moderate exacerbation health states.

The levels of healthcare resource use for 'Controlled asthma' in the reslizumab model was calculated using a weighted average of the 'Controlled asthma' and 'Partly controlled asthma' costs from Willson et al. As for the estimates of utility, the weights were based on the proportion of time spent in 'partly controlled asthma' (ACQ between 1 and 1.5) and 'controlled asthma' (ACQ <1) in the 3082 and 3083 trials (considering the two treatment arms): 49% of the time in asthma control corresponded to the definition of 'partly controlled' according to Willson.

Table 119: Comparison of live health state definitions in Willson et al and the current reslizumab model

Willson et al (118)	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

Willson et al (118)	Current model
Severe exacerbation with hospitalisation: Severe exacerbation + hospitalisation	provided by a UK expert, as described in Section 5.3.2

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

Unit costs (Table 120) were applied to the levels of healthcare resource use estimated by Willson. As for utility estimates, the mean cost of severe exacerbation was a weighted average of the cost of severe exacerbations leading and not leading to hospitalisation.

In the Willson study, the cycle length of the model was one week. A non-severe exacerbation was assumed to last one week whereas a severe exacerbation (with and without hospitalisation) lasted for 2 weeks. In order to calculate health state costs per cycle for the moderate and severe exacerbation states, we assumed that for one week the patient would experience an exacerbation (two weeks if the exacerbation was severe) and incur the cost of treating either a moderate or severe exacerbation. For the remaining time in that cycle, it was assumed that the patient would incur the costs of being in the uncontrolled asthma health state.

Table 120: Unit costs and medical resource use by health states (weekly)

Resource	Unit Cost	Health state			
		Controlled asthma	Uncontrolled asthma	Moderate exacerbation	Severe exacerbation
Outpatient visits (from survey)	**Cost per visit**	**No. of visits/patient/week**			
Visit to GP	£44.00 (PSSRU (140))	0.035	0.14	0.6	0.6302
Visit to nurse	£14.47 (PSSRU (140))	0.059	0.16	0.43	0.5139
Visit to specialist	£133.26 (Willson 2014 (118))	0.0243	0.094	0.094	0.2899
Home visit (from survey)	**Cost per visit**	**No. of visits/patient/week**			
Visit from GP	£113.00 (PSSRU, (140))	0.00507	0.025	0.034	0.1907
Visit from nurse	£37.33 (PSSRU, (140))	0	0	0	0.0047
Laboratory tests/procedures (from survey)	**Cost per test/ procedure**	**No. of procedures/patient/week**			
Spirometry	£28.20 (Willson 2014 (118))	0.027	0.049	0.29	0.46
Flu vaccine	£6.32 (Willson 2014 (118))	0.020	0.020	0	0
Desensitisation	£175.32 (Willson 2014 (118))	0.00612	0.0087	0	0
Inpatients resource used (from the clinical trials)	**Cost per episode**	**No. of events/patient/week**			
Hospitalisation	£758.98 (NHS ref costs (142))	0	0	0	0
Severe exacerbation-related hospitalisation	£1,629.97 (NHS ref costs (142))	0	0	0	0.0242
A&E visit only	£132.00 (NHS ref costs (142))	0	0	0	0.0218
A&E visit + hospitalisation	£1,761.97 (NHS ref costs (142))	0	0	0	0.0255
Ambulance + hospitalisation	£1,809.80 (NHS ref costs (142))	0	0	0	0.0014
Ambulance + A&E + hospitalisation	£1, 941.80 (NHS ref costs (142))	0	0	0	0.0027
Hospitalisation including ICU stay	£2,567.62 (NHS ref costs (142))	0	0	0	0.0081

Abbreviations: A&E, accident and emergency; GP, general practitioner; ICU, intensive care unit.

Table 121: Costs by health state – current model

Health state	Updated costs (2015)
Controlled asthma	£11.86
Uncontrolled asthma	£45.19
Moderate exacerbation	£70.36
Severe exacerbation	£649.56 Severe exacerbation not leading to hospitalisation: £234.21 Severe exacerbation not leading to hospitalisation: £1,906.54

Table 122: Health states and associated costs in the economic model

Health state	Item	Treatment arm					
		Reslizumab†		Best standard of care		Omalizumab†	
		Value	Reference	Value	Reference	Value	Reference
Uncontrolled asthma	Technology (25 mg vials)	# of 25 mg vials = **9.58** Cycle cost = [redacted]	Teva CSRs, Teva	£40.92	BNF legacy, 18 March 2016 Reslizumab studies 3082 and 3083	Mean number of 75 mg pre-filled syringes per cycle: 4.45 £569.98	INNOVATE trial (88) BNF
	Preparation, administration and monitoring	£54.08	Teva CSRs, PSSRU (140)	£0.00	Teva CSRs	£39.33 per administration 1.31 administration per cycle £51.64/cycle	PSSRU (140) INNOVATE trial (88)
	BSC	£40.92	BNF legacy, 18 March 2016 Reslizumab studies 3082 and 3083	–		£40.92	BNF legacy, 18 March 2016 Reslizumab studies 3082 and 3083
	Health state management	£45.19	Willson et al, 2014 (118)	£45.19	Willson et al, 2014 (118)	£45.19	Willson et al, 2014 (118)
	Total	[redacted]		**£86.11**		**£707.73**	
Controlled asthma	Technology	# of 25 mg vials = **9.58** Cycle cost = **£575**	Teva CSRs	£40.92	BNF legacy, 18 March 2016 Reslizumab studies 3082 and 3083	Mean number of 75 mg pre-filled syringes per cycle: 4.45 £569.98	INNOVATE trial (88) BNF
	Preparation, administration and monitoring	£54.08	Teva CSRs, PSSRU (140)	£0.00	Teva CSRs	£39.33 per administration 1.31 administration per cycle	PSSRU (140) INNOVATE trial (88)

						£51.64/cycle	
	BSC	£40.92	BNF legacy, 18 March 2016 Reslizumab studies 3082 and 3083	–		£40.92	BNF legacy, 18 March 2016 Reslizumab studies 3082 and 3083
	Health state management	£11.86	Willson et al, 2014 (118) PSSRU, 2015 (140)	£11.86	Willson et al, 2014 (118) PSSRU, 2015 (140)	£11.86	Willson et al, 2014 (118) PSSRU, 2015 (140)
	Total	[redacted]		**£52.78**		**£674.40**	
Moderate exacerbation	Technology	# of 25 mg vials = **9.58** Cycle cost = [redacted]	Teva CSRs	£40.92	BNF legacy, 18 March 2016 Reslizumab studies 3082 and 3083	Mean number of 75mg pre-filled syringes per cycle: 4.45 £569.98	INNOVATE trial (88) BNF
	Preparation, administration and monitoring	£54.08	Teva CSRs, PSSRU (140)		Teva CSRs BNF legacy, 18 March 2016 Reslizumab studies 3082 and 3083	£39.33 per administration 1.31 administration per cycle £51.64/cycle	PSSRU (140) INNOVATE trial (88)
	BSC	£40.92	BNF legacy, 18 March 2016 Reslizumab studies 3082 and 3083 Teva CSRs	–£0.00	Teva CSRs	£40.92	BNF legacy, 18 March 2016 Reslizumab studies 3082 and 3083
	Health state management	£70.36	Willson et al, 2014 (118) PSSRU, 2015 (140) BNF legacy,	£70.36	Willson et al, 2014 (118)PSSRU, 2015 (140)	£70.36	Willson et al, 2014 (118) PSSRU, 2015 (140) BNF legacy,

			18 March 2016 Reslizumab studies 3082 and 3083				18 March 2016 Reslizumab studies 3082 and 3083
	Total	[redacted]		**£111.28**		**£732.90**	
Severe exacerbation	Technology	# of 25 mg vials = **9.58** Cycle cost = [redacted]	Teva CSRs	£40.92	BNF legacy, 18 March 2016 Reslizumab studies 3082 and 3083 Willson et al, 2014 (118)	Mean number of 75mg pre-filled syringes per cycle: 4.45 £569.98	INNOVATE trial (88) BNF
	Preparation, administration and monitoring	£54.08	Teva CSRs, PSSRU (140)			£39.33 per administration 1.31 administration per cycle £51.64/cycle	PSSRU (140) INNOVATE trial (88)
	BSC	£40.92	BNF legacy, 18 March 2016 Reslizumab studies 3082 and 3083 Teva CSRs	–£0.00	Teva CSRs BNF legacy, 18 March 2016 Reslizumab studies 3082 and 3083	£40.92	BNF legacy, 18 March 2016 Reslizumab studies 3082 and 3083
	Health state management	£649.56	Willson et al, 2014 (118) PSSRU, 2015 (140)	£649.56	Willson et al, 2014 (118) PSSRU, 2015 (140)	£649.56	Willson et al, 2014 (118) PSSRU, 2015 (140)
	Total	[redacted]		**£690.48**		**£1,312.21**	

Abbreviations: BNF, British National Formulary; BSC, best standard of care; PSSRU, Personal Social Services Research Unit.

5.5.5 *Adverse reaction unit costs and resource use*

AEs were not included in the model (see Section 5.4.6).

5.5.6 *Miscellaneous unit costs and resource use*

Not applicable.

5.6 *Summary of base-case de novo analysis inputs and assumptions*

5.6.1 *Summary of base-case de novo analysis inputs*

A list of all variables used in the economic analysis is provided in Table 123.

Table 123: Summary of variables applied in the economic model

Variable	Value	Reference
Time horizon	60 years	NICE reference case (125)
Discount rates (costs and outcomes)	Costs: 3.5% Outcomes: 3.5%	
Age	46.8 years	Pooled analysis of reslizumab studies 3082 and 3083, adult patients at GINA Step 4/5 (76, 77)
% male	37%	
Average weight	75.2 kg	
% of severe exacerbations - reslizumab	76.3%	
% of severe exacerbations – BSC	81.8%	
% patients on reslizumab identified as non-responders at 16 weeks	13.2%	Analysis of reslizumab studies 3082 and 3083, patients with ≥2 prior exacerbations
% of severe exacerbations leading to hospitalisation across arms	24.8%	Data on file provided by clinical expert, UK cohort of severe asthma patients
% of non-responders to omalizumab at 16 weeks	43.5%	Omalizumab HTA (31)
Relative rate of exacerbations in responders to omalizumab vs BSC	0.373	Omalizumab HTA (31)
Reslizumab	[redacted]	Teva UK Limited, PAS price
Reslizumab	[redacted]	Teva UK Limited, PAS price
Omalizumab	£128.07 per 75 mg pre-filled syringe	BNF listed price
Fluticasone propionate + Salmeterol	£40.92	
Salbutamol	£1.50	
Specialist nurse	£59 per hour	NHS reference costs 2014/2015 (142)
Specialist visit	£146.53	
Administrations of omalizumab per cycle	1.31	Omalizumab HTA (31)

Variable	Value	Reference
Time for administration and monitoring	Omalizumab: 40 mins Reslizumab: 55 mins	Clinical experts
Cost per health state (excluding drug costs)		
Controlled asthma	£11.86	Willson et al, 2014 (118) and unit costs taken from NHS reference costs, PSSRU and BNF – see Table 120 and Table 122
Uncontrolled asthma	£45.19	
Moderate exacerbation	£70.36	
Severe exacerbation	£649.56	
Utility per health state		
Controlled asthma	0.920	Lloyd et al, 2007 (129) Willson et al, 2014 (118)
Uncontrolled asthma	0.728	
Moderate exacerbation	0.57	
Severe exacerbation	0.33	

Abbreviations: BNF, British National Formulary; CI, confidence interval; NHS, National Health Service.

5.6.2 *Assumptions*

Discontinuation at 16 weeks:

The model is structured in a way that biologic treatment effect is assessed after 16 weeks. If a patient fails to show a significant clinical response, then he/she may be taken off biologic treatment. For reslizumab the proportion of responders is predicated on the output of an algorithm developed by Teva Pharmaceutical Industries Limited (see Section 5.2.2).

The proportion of patients who respond to omalizumab has been taken from the omalizumab MTA submission (31). The trial from which this figure was taken was carried out a number of years ago and is obviously subject to fluctuation depending on the population and the physician carrying out the assessment.

Discontinuation of patients who are suffering from uncontrolled asthma or in the exacerbation states continuously for 12 months:

In this model it is assumed that patients who remain in the 'uncontrolled asthma', 'moderate exacerbation', or 'severe exacerbation' health states for a consecutive period of 12 months will discontinue treatment. Although this rule has been validated with UK clinical experts, the exact definition of uncontrolled asthma is likely to differ from the definition used in the model based on an [redacted].

Health state utilities taken from Lloyd et al (129):

In the current model, the utilities for health states were taken from a prospective study conducted in the UK at four specialty asthma centres. Patients had moderate to severe asthma (BTS/SIGN Step 4/5) defined as those managed with at least one high dose formulation of ICS plus LABA, or any leukotriene-receptor antagonist.

The figure for uncontrolled asthma was taken directly from the study. However, the utility used for 'controlled asthma' is a weighted average of the 'controlled' and 'partly controlled' health states in Lloyd et al (see Section 5.4.7).

Relative treatment effect of reslizumab taken from trials

Efficacy data relating to reslizumab comes directly from the pivotal clinical trials (76, 77). In order to adjust the risk of exacerbation in the BSC arm to the population of interest, a multiplicative factor is applied. This increased risk is then applied to the probabilities in the reslizumab arm as well. **BSC treatment is comprised solely of the Fluticasone Propionate + Salmeterol (FP + S) combination:**

In terms of BSC dosing, the model is set-up to account for a patient taking 0.79 mg of FP per day. This is an assumption and the figure has been directly taken from the pooled analysis of the pivotal trials.

5.7 *Base-case results*

The base case analysis focused on the comparison of reslizumab with BSC in patients aged ≥18 years at GINA Steps 4 and 5 who had experienced at least three exacerbations in the year preceding baseline in the pivotal clinical trials. The results of the base case analysis are presented in Table 124.

Table 124: Base case cost-effectiveness results: Patients with a history of ≥3 exacerbations

Treatment arm	Total			Incremental			ICER/ QALYs, £	ICER / LYG, £
	Costs, £	LYG	QALYs	Costs, £	LYG	QALYs		
BSC	[redacted]	[redacted]	[redacted]					
Reslizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,907	£22,367

Abbreviations: BSC, best standard of care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

In patients with severe persistent allergic IgE-mediated eosinophilic asthma, omalizumab is also a relevant comparator. The results of this analysis are presented in Table 125.

Table 125: Base case cost-effectiveness results: Patients with severe persistent allergic IgE-mediated eosinophilic asthma and a history of ≥3 exacerbations

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]	£33,254	£33,254
Reslizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,643	£24,907

Abbreviations: BSC, best standard of care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

5.7.1 *Clinical outcomes from the model*

To ascertain the number of exacerbations predicted by the model, we added together the number of moderate exacerbations and the number of severe exacerbations that a patient suffered over a life-time time horizon.

The predicted number of exacerbation-related deaths is dependent on the transition probabilities from a severe exacerbation to asthma-related mortality. The two pivotal clinical studies used to inform this model only ran for a total of one year each. During this time, neither study reported an asthma-related death. Given this disparity in time horizons and adjustment in the rate of exacerbations, the absolute rates of exacerbation are not directly comparable.

However, the relative rate of exacerbation of reslizumab (for patients still on treatment) versus BSC was estimated at 0.42; which is directly in line with the results of the meta-analysis: 0.44 [0.35; 0.56] from the fixed effect model (95).

The progression of patients over time and by treatment arm is presented in the graphs below.

Figure 40. Markov trace: asthma control over time

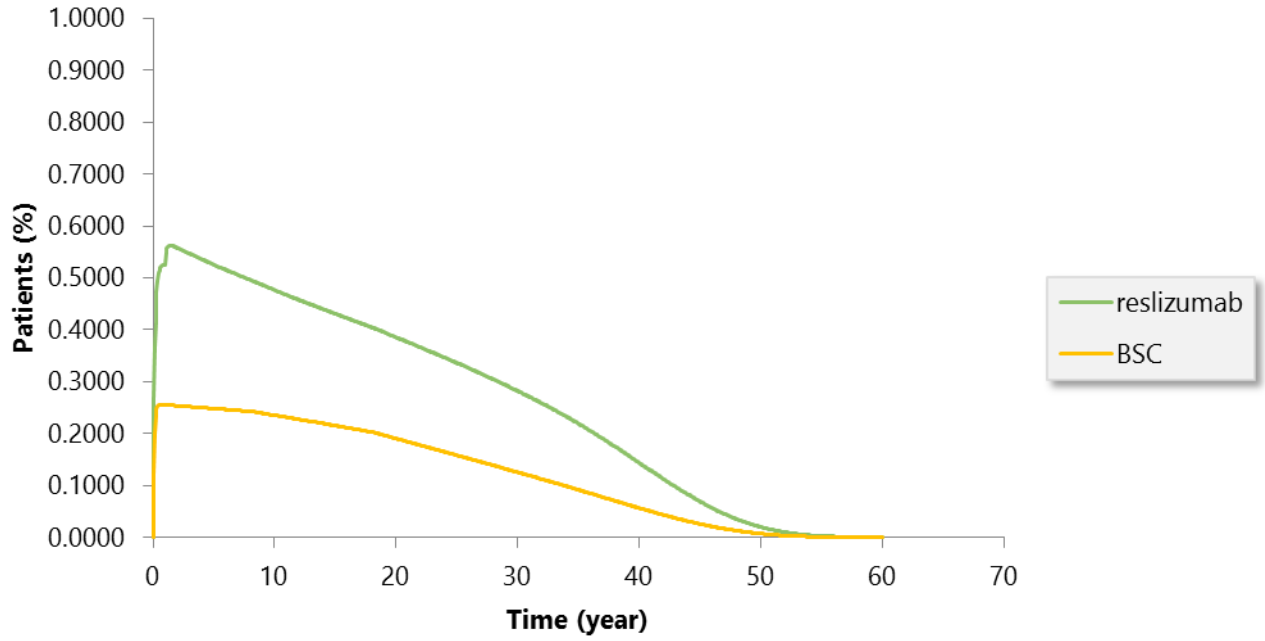


Figure 41. Markov trace: moderate exacerbations over time

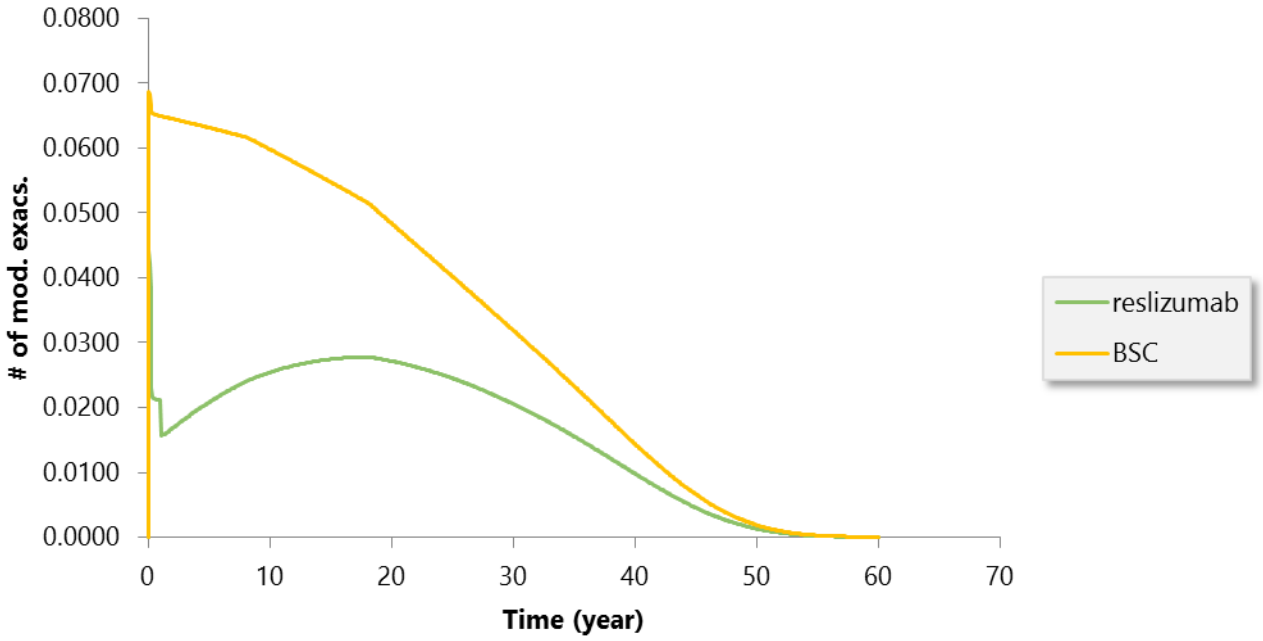


Figure 42. Markov trace: severe exacerbations over time

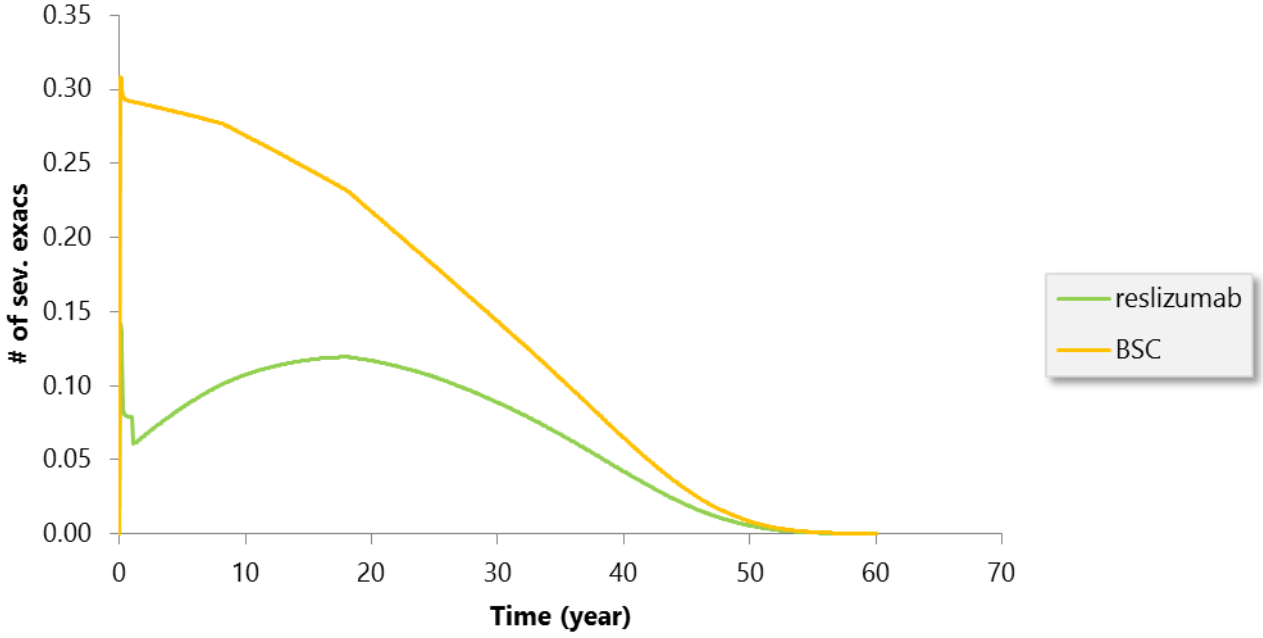


Figure 43. Markov trace: cumulative asthma-related death

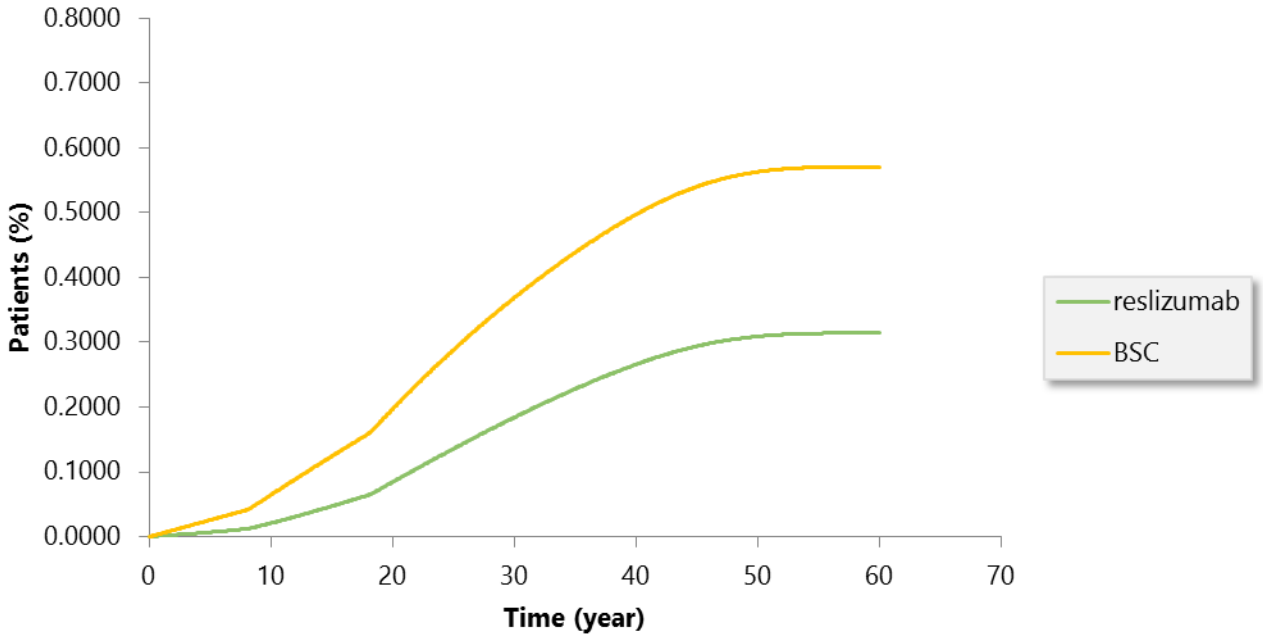
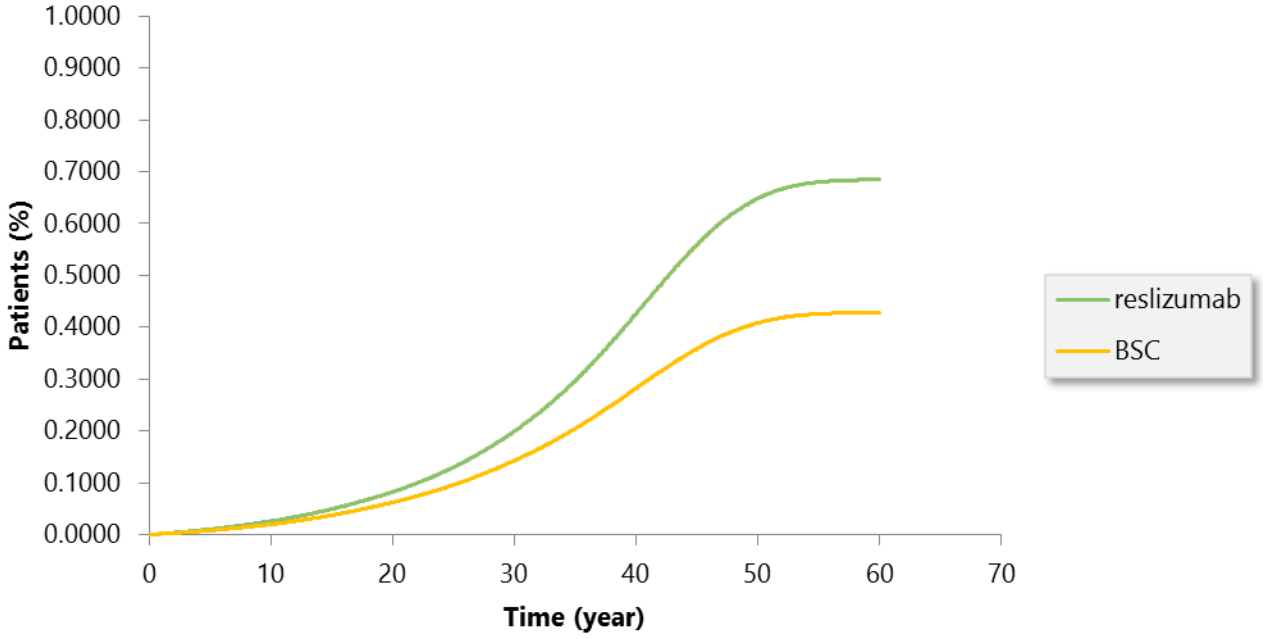


Figure 44. Markov trace: background death



Over a lifetime horizon, the model predicted that patients treated with reslizumab would spend an average of 15.77 years in controlled asthma compared with 7.4 years for BSC.

Table 126: Summary of model results compared with clinical data

Outcome	Clinical trial result	Model result	
		reslizumab	BSC
Mean annual number of exacerbations	4.67 in patients having experienced ≥3 exacerbations	1.96	4.67
Relative rate: Meta-analysis of reslizumab vs BSC (95)	0.44 [0.35;0.56]	0.42	
Number of exacerbation-related deaths	NA	0.31	0.57

Abbreviations: BSC, best standard of care.

The QALYs accrued over time were also calculated through the use of the Markov trace. Health state specific utilities were weighted by the proportion of patients in that health state. Utilities were simultaneously adjusted in order to be applicable to a single 4 week cycle. These values were then summed across all four living health states and a QALYs per cycle total was derived. The QALYs per cycle were then added cumulatively to provide a total number of QALYs per treatment arm over the time horizon. In depth QALYs results are provided in Table 127.

5.7.2 *Disaggregated results of the base case incremental cost effectiveness analysis*

Health state utilities were cycle-adjusted and weighted by the proportion of the patients in each of the health states per cycle. The values purporting to each health state were then summed cumulatively to provide a total number of QALYs for each of the treatment arms featured in the base case analysis.

As mentioned earlier, a discount rate of 3.5% was applied to both costs and health outcomes in line with the NICE reference case. The discounted values are reported in Table 127.

Table 127: Summary of QALY gain by health state: reslizumab vs BSC (discounted at 3.5%)

Health state	QALY intervention reslizumab	QALY comparator BSC	Increment	% increment
Controlled asthma	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled asthma	[redacted]	[redacted]	[redacted]	[redacted]
Moderate exacerbation	[redacted]	[redacted]	[redacted]	[redacted]
Severe exacerbation	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL	[redacted]	[redacted]	[redacted]	[redacted]

The results for the comparison of reslizumab with omalizumab in patients with severe persistent allergic IgE-mediated eosinophilic asthma having an annual rate of 3 or more exacerbations are presented in Table 128.

Table 128: Summary of QALY gain by health state in patients with severe allergic asthma: reslizumab vs omalizumab (discounted at 3.5%)

Health state	QALY intervention reslizumab	QALY comparator omalizumab	Increment	% increment
Controlled asthma	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled asthma	[redacted]	[redacted]	[redacted]	[redacted]
Moderate exacerbation	[redacted]	[redacted]	[redacted]	[redacted]
Severe exacerbation	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL	[redacted]	[redacted]	[redacted]	[redacted]

Similarly, the costs by health state are presented in Table 129.

Table 129: Summary of predicted total costs by health state

Health state	Costs intervention reslizumab	Costs comparator BSC	Increment	% increment
Controlled asthma	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled asthma	[redacted]	[redacted]	[redacted]	[redacted]
Moderate exacerbation	[redacted]	[redacted]	[redacted]	[redacted]
Severe exacerbation	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL	[redacted]	[redacted]	[redacted]	[redacted]

The results for the comparison of reslizumab with omalizumab in patients with severe persistent allergic IgE-mediated eosinophilic asthma having an annual rate of 3 or more exacerbations are presented in Table 130.

Table 130: Summary of costs gain by health state in patients with severe allergic asthma: reslizumab vs omalizumab (discounted at 3.5%)

Health state	Costs intervention reslizumab	Costs comparator omalizumab	Increment	% increment
Controlled asthma	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled asthma	[redacted]	[redacted]	[redacted]	[redacted]
Moderate exacerbation	[redacted]	[redacted]	[redacted]	[redacted]
Severe exacerbation	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL	[redacted]	[redacted]	[redacted]	[redacted]

5.8 *Sensitivity analyses*

5.8.1 *Probabilistic sensitivity analysis*

5.8.1.1 Inputs

The variables subjected to probabilistic sensitivity analysis are outlined in Table 131. For the average patient age and weight, we used the values from the pooled analysis of the pivotal clinical trials and assumed that these parameters were normally distributed. In order to draw estimates for the Percentage of females, Proportion of severe exacerbations, and Transition probability (for both reslizumab and BSC), beta distributions were used, and their parameters α and β were estimated based on the number of occurrences / non-occurrences of the event in the pooled analysis of the pivotal clinical trials (76, 77).

To incorporate health state-specific utilities into the analysis a beta distribution was chosen and the confidence intervals reported in the original paper by Willson et al (118) were used in order to derive alpha and beta.

Health state costs were assumed to vary based on a gamma distribution. As the uncertainty related to costs was assumed to be larger uncertainty than the data presented in the study, the confidence intervals reported by Willson et al were not used. The parameters of the gamma distribution were based on the assumption that the standard deviation for each cost was assumed to be 10% of the adjusted mean, so that the lower/upper limit of the 95% confidence intervals are 20% lower/higher than the mean estimates.

The transition probabilities beta distributions were based on a sequence of conditional probabilities, similar to a dirichlet distribution. The transition probabilities distributions to uncontrolled asthma were calculated using the number of occurrences of this event (α) and number of non-occurrences of this event (β), taken from the clinical trials. The probabilities of being controlled, within non-uncontrolled patients was then simulated and the transition probability derived from it. The transition probability to moderate exacerbation was based on the probability of exacerbation and the proportion of

moderate exacerbation. The probability of severe exacerbation was defined as one minus the previous other transitions. This method was applied for the transitions from all the other health states across the reslizumab and BSC treatment arms.

A log normal distribution was used for the following parameters: the relative risks of exacerbation pre- and post-16 weeks of omalizumab versus BSC, the odds ratio for asthma related mortality. Data from the meta-analysis and the INNOVATE trial were used to derive the coefficients of the lognormal distributions for the relative risks. The Roberts publication was used for the asthma mortality ORs.

Uniform distributions were assumed for the percentage of severe exacerbations leading to hospitalisations, the percentage of moderate exacerbations for reslizumab (and omalizumab) and BSC, as well as the percentage of early responders for reslizumab. A range of variation of 40% of the mean value was used for each parameter

The details of distributions for each parameter included in the PSA are presented in Table 131 and Table 132.

Table 131: PSA parameter inputs

Parameter	Mean	Alpha (α)	Beta (β)	Distribution
Percentage of females	63% (76, 77)	597	396	Beta
Patient age at model entry	46.80 (76, 77)	N/A	N/A	Normal
Mean patient weight	75.2 (76, 77)	N/A	N/A	Normal
Cost of 'Controlled asthma' (cycle)	£11.86 (118)	100	0.1186	Gamma
Cost of 'Uncontrolled asthma' (cycle)	£45.19 (118)	100	0.4519	Gamma
Cost of 'Moderate exacerbation' (cycle)	£70.36 (118)	100	0.7036	Gamma
Cost of 'severe exacerbation' (cycle)	£649.56 (118)	100	6.495599346	Gamma
Utility of 'Controlled asthma' (cycle)	0.92 (118)	464.61	31.24	Beta
Utility of 'Uncontrolled asthma' (cycle)	0.73 (118)	2562.04	957.25	Beta
Utility of 'Moderate exacerbation' (cycle)	0.57 (118)	1175.32	886.64	Beta
Utility of 'severe exacerbation' (cycle)	0.33 (118)	613.78	1246.17	Beta
% early non responders - reslizumab	13%	0.08178	0.18178	Uniform
Proportion of moderate exacerbations (reslizumab)	24%	0.1896	0.2844	Uniform
Proportion of moderate exacerbations (BSC)	18%	0.1456	0.2184	Uniform
Proportion of severe exacerbations leading to	24.84% (76, 77)	0.19869	0.29804	Uniform

hospitalisation				
BSC annual rate of exacerbations	2.15	1.99	2.83	Uniform
RR omalizumab vs BSC pre 16 weeks	0.82	–0.2659	0.36715	Lognormal
RR omalizumab vs BSC post 16 weeks	0.37	–1.0845	0.44344	Lognormal
OR death 25-34	1.1	0.05186	0.2948	Lognormal
OR death 35-44	1.4	0.3071	0.24238	Lognormal
OR death 45-54	2.4	0.86714	0.12906	Lognormal
OR death 55-64	6.3	1.82544	0.17383	Lognormal
OR death 65+	12.3	2.50578	0.08736	Lognormal
Reslizumab transition probabilities • Baseline – Week 16 • Week 16 – Week 52 • Post-52 weeks	N/A	N/A	N/A	Beta
BSC transition probabilities • Baseline – Week 52 • Post-52 weeks	N/A	N/A	N/A	Beta

Abbreviations: BSC, best standard of care; N/A, not applicable; OR, odds ratio.

Table 132: Transition probabilities: Coefficient values for beta distributions of conditional probabilities

Arm	Period	Probability	Alpha	Beta
Reslizumab	BL to 16	Uncontrolled to uncontrolled	190.0	290.0
Reslizumab	BL to 16	Uncontrolled to controlled | not uncontrolled	94.0	100.0
Reslizumab	BL to 16	Uncontrolled to moderate exacerbation | neither uncontrolled nor controlled	1.4	4.6
Reslizumab	BL to 16	Uncontrolled to uncontrolled	45.0	179.0
Reslizumab	BL to 16	Uncontrolled to controlled | not uncontrolled	131.0	134.0
Reslizumab	BL to 16	Uncontrolled to moderate exacerbation | neither uncontrolled nor controlled	0.7	2.3
Reslizumab	BL to 16	Uncontrolled to uncontrolled	15.0	24.0
Reslizumab	BL to 16	Uncontrolled to controlled | not uncontrolled	5.0	9.0
Reslizumab	BL to 16	Uncontrolled to moderate exacerbation | neither uncontrolled nor controlled	0.9	3.1
Reslizumab	BL to 16	Uncontrolled to uncontrolled	15.0	24.0
Reslizumab	BL to 16	Uncontrolled to controlled | not uncontrolled	5.0	9.0
Reslizumab	BL to 16	Uncontrolled to moderate exacerbation | neither uncontrolled nor controlled	0.9	3.1

Reslizumab	16 to 52	Uncontrolled to uncontrolled	308.0	424.0
Reslizumab	16 to 52	Uncontrolled to controlled | not uncontrolled	101.0	116.0
Reslizumab	16 to 52	Uncontrolled to moderate exacerbation | neither uncontrolled nor controlled	3.6	11.4
Reslizumab	16 to 52	Uncontrolled to uncontrolled	83.0	540.0
Reslizumab	16 to 52	Uncontrolled to controlled | not uncontrolled	446.0	457.0
Reslizumab	16 to 52	Uncontrolled to moderate exacerbation | neither uncontrolled nor controlled	2.6	8.4
Reslizumab	16 to 52	Uncontrolled to uncontrolled	15.0	31.0
Reslizumab	16 to 52	Uncontrolled to controlled | not uncontrolled	14.0	16.0
Reslizumab	16 to 52	Uncontrolled to moderate exacerbation | neither uncontrolled nor controlled	0.5	1.5
Reslizumab	16 to 52	Uncontrolled to uncontrolled	15.0	31.0
Reslizumab	16 to 52	Uncontrolled to controlled | not uncontrolled	14.0	16.0
Reslizumab	16 to 52	Uncontrolled to moderate exacerbation | neither uncontrolled nor controlled	0.5	1.5
Reslizumab	Post 52	Uncontrolled to uncontrolled	263.0	361.0
Reslizumab	Post 52	Uncontrolled to controlled | not uncontrolled	92.0	98.0
Reslizumab	Post 52	Uncontrolled to moderate exacerbation | neither uncontrolled nor controlled	1.4	4.6
Reslizumab	Post 52	Uncontrolled to uncontrolled	74.0	520.0
Reslizumab	Post 52	Uncontrolled to controlled | not uncontrolled	437.0	446.0
Reslizumab	Post 52	Uncontrolled to moderate exacerbation | neither uncontrolled nor controlled	2.1	6.9
Reslizumab	Post 52	Uncontrolled to uncontrolled	7.0	19.0
Reslizumab	Post 52	Uncontrolled to controlled | not uncontrolled	10.0	12.0
Reslizumab	Post 52	Uncontrolled to moderate exacerbation | neither uncontrolled nor controlled	0.5	1.5
Reslizumab	Post 52	Uncontrolled to uncontrolled	7.0	19.0
Reslizumab	Post 52	Uncontrolled to controlled | not uncontrolled	10.0	12.0
Reslizumab	Post 52	Uncontrolled to moderate exacerbation | neither uncontrolled nor controlled	0.5	1.5
BSC	0 to 52	Uncontrolled to uncontrolled	670.0	1014.0
BSC	0 to 52	Uncontrolled to controlled | not uncontrolled	166.0	344.0
BSC	0 to 52	Uncontrolled to moderate exacerbation | neither uncontrolled nor controlled	42.2	135.8

BSC	0 to 52	Uncontrolled to uncontrolled	129.0	555.0
BSC	0 to 52	Uncontrolled to controlled | not uncontrolled	360.0	426.0
BSC	0 to 52	Uncontrolled to moderate exacerbation | neither uncontrolled nor controlled	15.6	50.4
BSC	0 to 52	Uncontrolled to uncontrolled	153.0	281.0
BSC	0 to 52	Uncontrolled to controlled | not uncontrolled	74.0	128.0
BSC	0 to 52	Uncontrolled to moderate exacerbation | neither uncontrolled nor controlled	12.8	41.2
BSC	0 to 52	Uncontrolled to uncontrolled	153.0	281.0
BSC	0 to 52	Uncontrolled to controlled | not uncontrolled	74.0	128.0
BSC	0 to 52	Uncontrolled to moderate exacerbation | neither uncontrolled nor controlled	12.8	41.2
BSC	Post 52	Uncontrolled to uncontrolled	670.0	1014.0
BSC	Post 52	Uncontrolled to controlled | not uncontrolled	166.0	344.0
BSC	Post 52	Uncontrolled to moderate exacerbation | neither uncontrolled nor controlled	42.2	135.8
BSC	Post 52	Uncontrolled to uncontrolled	129.0	555.0
BSC	Post 52	Uncontrolled to controlled | not uncontrolled	360.0	426.0
BSC	Post 52	Uncontrolled to moderate exacerbation | neither uncontrolled nor controlled	15.6	50.4
BSC	Post 52	Uncontrolled to uncontrolled	153.0	281.0
BSC	Post 52	Uncontrolled to controlled | not uncontrolled	74.0	128.0
BSC	Post 52	Uncontrolled to moderate exacerbation | neither uncontrolled nor controlled	12.8	41.2
BSC	Post 52	Uncontrolled to uncontrolled	153.0	281.0
BSC	Post 52	Uncontrolled to controlled | not uncontrolled	74.0	128.0
BSC	Post 52	Uncontrolled to moderate exacerbation | neither uncontrolled nor controlled	12.8	41.2

Abbreviations: BL, baseline; BSC, best standard of care.

5.8.1.2 Results

The PSA was carried out over a total of 1,000 iterations, the descriptive statistics of the results are presented in Table 133 and Table 134.

The PSA of the population of patients with a history of ≥3 exacerbations produced a mean ICER of £32,828 (mean incremental costs over mean incremental QALYs) when reslizumab was compared with BSC. The PSA of the population of patients with severe persistent allergic IgE-mediated eosinophilic asthma and a history of ≥3 exacerbations produced a mean ICER of £20,930 when reslizumab was compared with omalizumab.

Table 133: Descriptive statistics of PSA results

	Reslizumab		BSC		Omalizumab	
	Base case	**PSA**	**Base case**	**PSA**	**Base case**	**PSA**
Total costs						
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min.		[redacted]		[redacted]		[redacted]
Max.		[redacted]		[redacted]		[redacted]
SD		[redacted]		[redacted]		[redacted]
2.5% percentile		[redacted]		[redacted]		[redacted]
97.5% percentile		[redacted]		[redacted]		[redacted]
Total QALYs						
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min.		[redacted]		[redacted]		[redacted]
Max.		[redacted]		[redacted]		[redacted]
SD		[redacted]		[redacted]		[redacted]
2.5% percentile		[redacted]		[redacted]		[redacted]
97.5% percentile		[redacted]		[redacted]		[redacted]

Table 134: Descriptive statistics of PSA ICERs

	Reslizumab vs. BSC		Reslizumab vs. omalizumab	
	Base case	**PSA**	**Base case**	**PSA**
ICER				
Mean	£24,907	£32,828	£16,643	£20,930
Minimum		Dominated		Dominated
Maximum		£2,363,656		£22,167,615
SD		£202,249		1,000,792
2.5% percentile		Dominated		Dominated
97.5% percentile		202,397		£123,842

The cost-effectiveness planes for reslizumab versus BSC and reslizumab versus omalizumab are presented below.

Figure 45: Cost-effectiveness plane: reslizumab vs BSC

Figure 46: Cost-effectiveness plane: reslizumab vs omalizumab

The cost-effectiveness acceptability curves are presented below. The curves illustrate the probability of a treatment being cost-effective at any given willingness-to-pay threshold ranging from £0 to £150,000.

- When compared with BSC only, reslizumab has a probability of 41.8% of being the optimal treatment at a threshold of £30,000.
- When compared with omalizumab, reslizumab has a probability of 38.6% of being the optimal treatment at a threshold of £30,000.

This PSA can be described as conservative due to the distributions used. BSC rate of exacerbations was a key driver in the model and as we varied this parameter using a uniform distribution, there was a high level of uncertainty. In addition, given the model structure, transition probabilities were drawn independently for reslizumab and BSC, rather than drawing the relative treatment effect, thereby leading to higher levels of uncertainty.

Figure 47: Cost-effectiveness acceptability curve: Reslizumab vs BSC

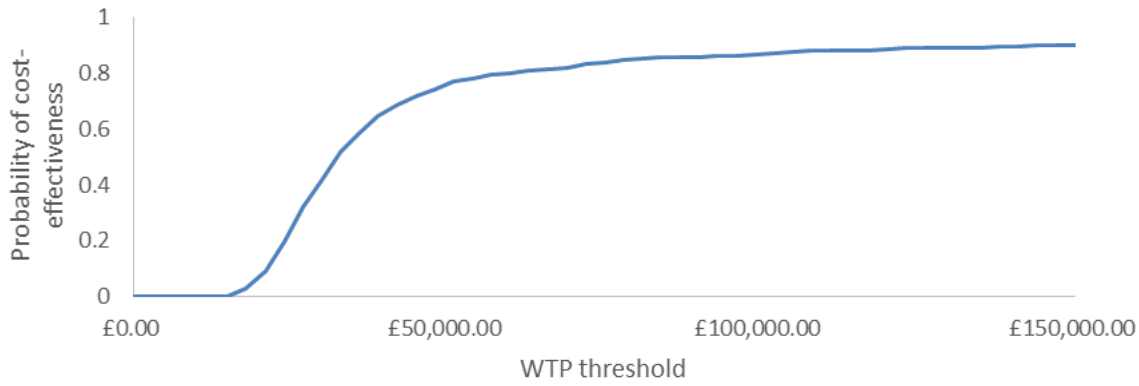
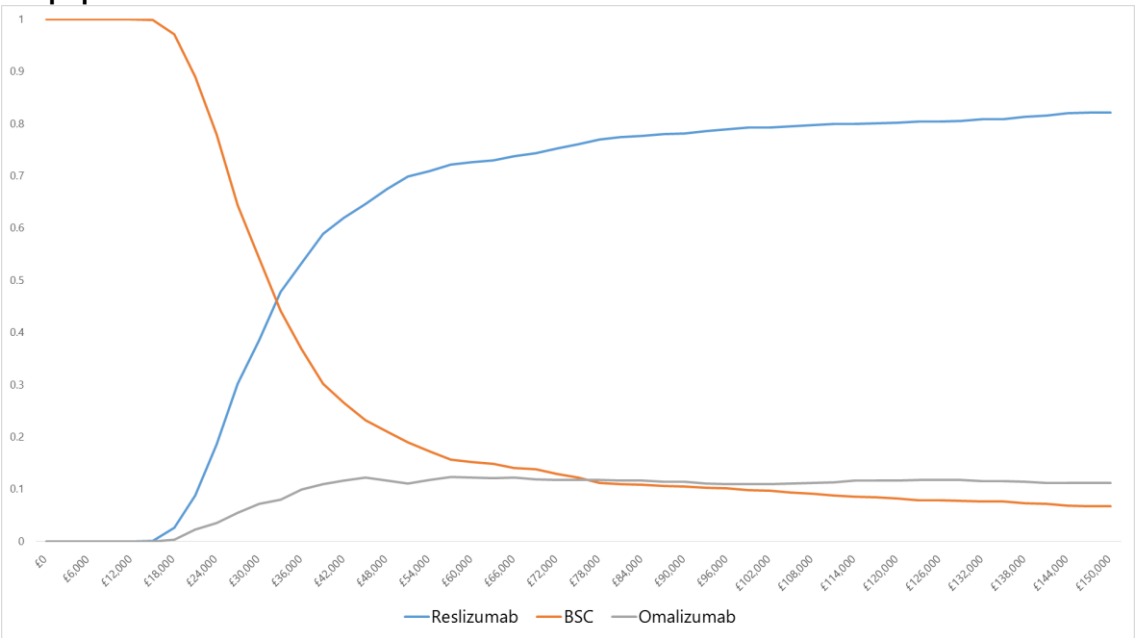


Figure 48: Cost-effectiveness acceptability curve: Severe persistent IgE-mediated asthma subpopulation



5.8.1.3 Discussion of variation between base case and PSA results

The mean costs and QALYs for each treatment arm generated by the PSA are in line with those produced by the base case analysis. The largest percentage change when comparing the mean costs results was -4% (BSC arm). In terms of QALYS, the largest change was in the reslizumab arm which produced a difference of 0.74 QALYs. This difference equates to an approximate 5% change.

5.8.2 *Deterministic sensitivity analysis*

5.8.2.1 Inputs

The following model inputs were varied as part of the deterministic sensitivity analysis (DSA). When confidence intervals were not available from the original source used to estimate the base case value and/or when the source of variability was thought to be beyond the study source, parameters were varied by +20% and –20% compared with the base case estimate.

Table 135: Inputs varied in the DSA

Parameter	Base case	Min–Max	Source
Time horizon	60	5–60	
Discount rate - (costs and QALYs)	3.5%	0–5%	
Proportion of patients identified as early non responders to reslizumab	13.2%	8.2–18.2%	Base case +/- 5 points
Percentage of females	63%	50.5–75.6%	Base case +/- 20%
Patient age	46.8	37.4–56.2	
Proportion of severe exacerbations leading to hospitalisation	24.84%	19.9–29.8%	
Proportion of moderate exacerbations (vs severe) - reslizumab/omalizumab	23.7%	19.0–28.4%	
Proportion of moderate exacerbations (vs severe) - BSC	18.2%	14.6–21.8%	
Weight/mean number of vials: +/-0.5 vials corresponding to a decrease/increase in the weight of 4 kg.	9.58	9.08-10.08	Assumption
Mean annual rate of exacerbations in the BSC arm	4.67	4.29-5.05	95% CI reported in the 3082 and 3083 trials (76, 77)
Omalizumab: RR of exacerbations vs BSC for responders (pre 16 weeks)	0.82	0.41-1.61	Norman et al, 2013 (121)
Omalizumab: RR of exacerbations vs BSC for all treated patients (post 16 weeks)	0.373	0.2653-0.5245	
Cost – controlled asthma	£11.18	£9.49 – £14.23	
Cost – uncontrolled asthma	£45.19	£36.15 – £54.228	

Cost – moderate exacerbation	£70.36	£56.29 – £84.43	
Cost – severe exacerbation	£649.56	£519.65 – £779.47	
Utility – controlled asthma	0.920	0.901–0.943	Lloyd et al, 2007 (129) Willson et al, 2014 (118)
Utility – uncontrolled asthma	0.728	0.707–0.749	
Utility – moderate exacerbation	0.57	0.549–0.591	
Utility – severe exacerbation	0.33	0.309–0.351	
OR – death 25-34	1.1	0.6–0.22	Roberts et al, 2013 (21)
OR – death 35-44	1.4	0.7–2.7	
OR – death 45-54	2.4	1.3–4.4	
OR – death 55-64	6.3	3.6–11.1	
OR – death 65+	12.3	7.1–21.3	

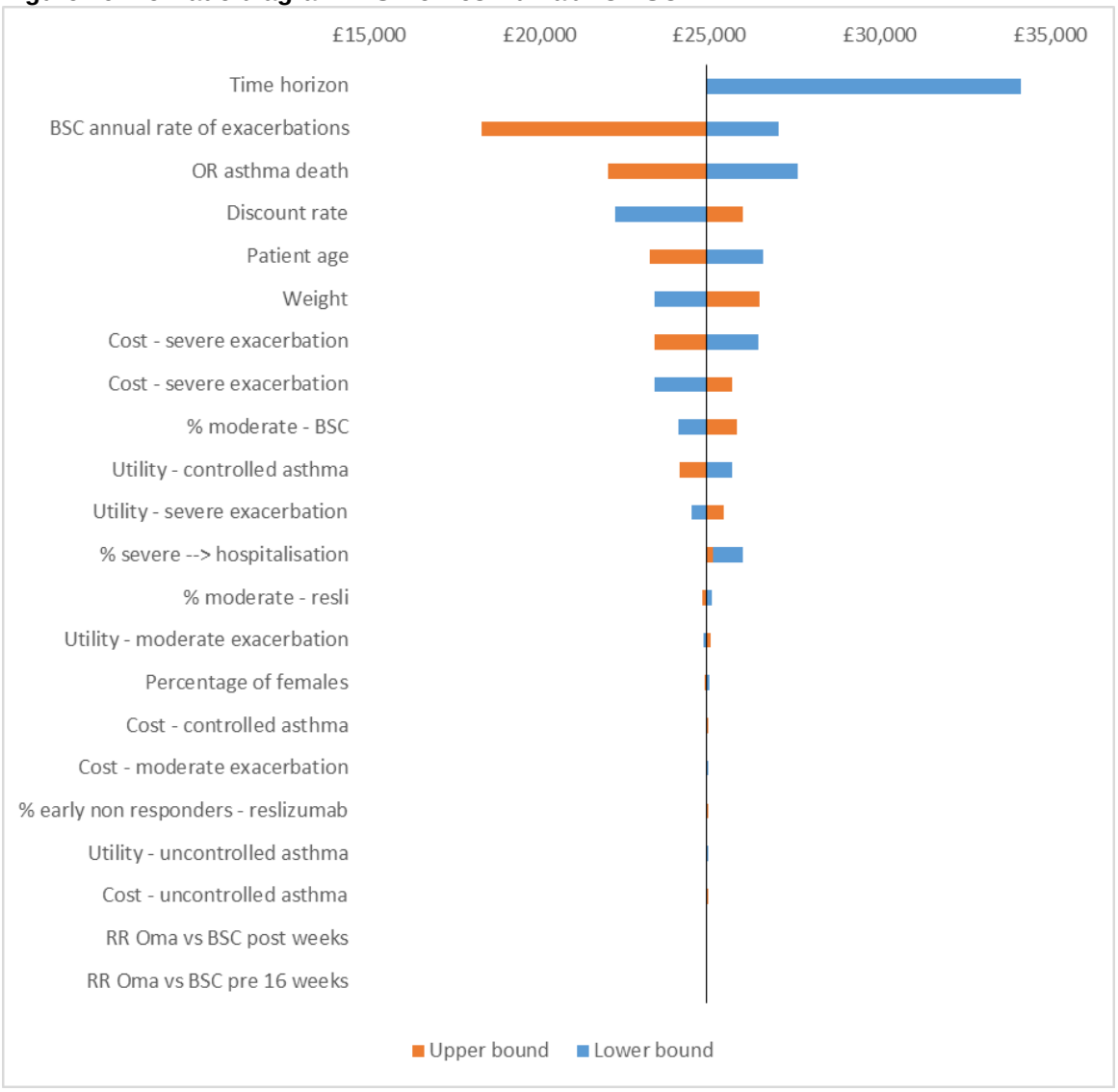
Abbreviations: BSC, best standard of care; CI, confidence interval; DSA, deterministic sensitivity analysis; OR, odds ratio; QALY, quality-adjusted life year; RR, relative risk.

5.8.2.2 Results

The base case ICER for the comparison of reslizumab with BSC varied from £18,275/QALY to £34,140/QALY. Results were most sensitive to the baseline risk of exacerbations (£27,015 to £18,275 when setting the annual rate of exacerbations for BSC to the lower and upper values), a shorter time-horizon (5 years), which was associated with the highest ICER (£34,140/QALY) and the odds ratio for asthma death (setting the ratio to the lower and upper bounds produced ICERs of £27,589 and £22,017, respectively)

A tornado diagram of the ICERs generated for the reslizumab versus BSC comparison is presented in Figure 49.

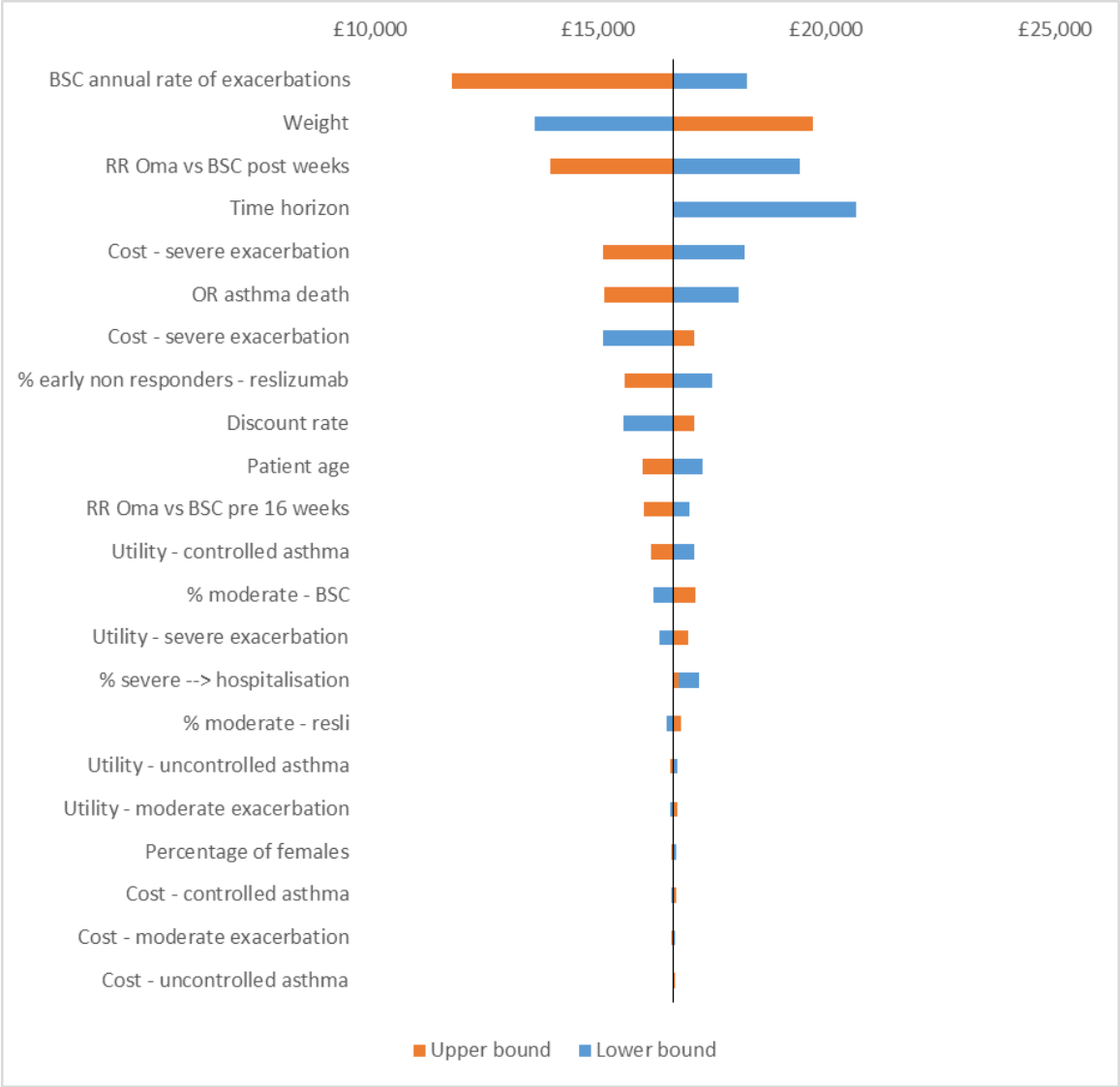
Figure 49. Tornado diagram: DSA of reslizumab vs BSC



With respect to the DSA evaluating reslizumab versus omalizumab, the base case ICER varied from £11,774 to £20,655. Results were most sensitive to patient weight (£13,587 and £19,699 when setting average patient weight to the lower and upper bounds), relative risk for omalizumab versus BSC in the post-52 week time period (ICERs varied from £19,413 to £13,939 in this scenario), and the annual rate of exacerbations in the BSC arm (between £18,237 and £11,774 when the parameter was set to its lower and upper bounds, respectively).

A tornado diagram of the ICERs generated for the reslizumab versus omalizumab comparison is presented in Figure 50.

Figure 50: Tornado diagram: DSA of reslizumab vs omalizumab



5.8.3 *Scenario analysis*

Two scenario analyses were conducted to assess the impact of vial size and vial sharing. Assuming no vial sharing and the use of only 100 mg vials led to the results presented in Table 136. The use of vial sharing generated the results presented in Table 137.

Table 136: Scenario analysis: Use of 100 mg vials, no vial sharing

Treatment arm	Total			Incremental			ICER/ QALY, £
	Costs, £	LYG	QALYs	Costs, £	LYG	QALYs	
BSC	[redacted]	[redacted]	[redacted]				
Reslizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,330

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 137: Scenario analysis: Use of 100 mg vials, vial sharing

Treatment arm	Total			Incremental			ICER/ QALY, £
	Costs, £	LYG	QALYs	Costs, £	LYG	QALYs	
BSC	[redacted]	[redacted]	[redacted]				
Reslizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,189

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

A third scenario analysis was conducted, whereby a different source of utilities was used for the 'Controlled asthma' and 'Uncontrolled asthma' health states. In the base case analysis, utilities were primarily based on those values reported in Willson (118). As described in Section 5.4.2, throughout the clinical trials, patients were asked to complete the AQLQ cyclically. Using this data and an algorithm published by the University of Sheffield (124), it was possible to derive EQ-5D data (and therefore utilities) indirectly from the clinical trials. The results of this exploratory analysis are presented in Table 138.

Table 138: Scenario analysis: Use of uncontrolled and controlled asthma utilities derived from mapping clinical trial data

Treatment arm	Total			Incremental			ICER/ QALY, £
	Costs, £	LYG	QALYs	Costs, £	LYG	QALYs	
BSC	[redacted]	[redacted]	[redacted]				
Reslizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,839

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

The confidentiality of the omalizumab patient access scheme means that the true price of omalizumab is largely unknown. As a result, we performed scenario analyses in which we varied the omalizumab list price by 20%, 30% and 40%. The results of this analysis are presented below.

Table 139 Scenario analysis: 20% discount of omalizumab list price

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]	£25,832	£25,832
Reslizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,992	£24,907

Table 140 Scenario analysis: 30% discount of omalizumab list price

Treatment arm	Total			Incremental			ICER/ QALYs, £ increment	ICER/ QALYs, £ vs BSC
	Costs, £	LY	QALYs	Costs, £	LYG	QALYs		
BSC	[redacted]	[redacted]	[redacted]					

Treatment arm	Total			Incremental			ICER/ QALYs, £ increment	ICER/ QALYs, £ vs BSC
	Costs, £	LY	QALYs	Costs, £	LYG	QALYs		
Omalizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,121	£22,121
Reslizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,666	£24,907

Table 141 Scenario analysis: 40% discount of omalizumab list price

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]	£18,409	£18,409
Reslizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,340	£24,907

5.8.4 *Summary of sensitivity analyses results*

Results of the one-way sensitivity analysis demonstrate that the model drivers were the time horizon, baseline risk of exacerbations, odds ratios for asthma-related mortality following severe exacerbation, discount rates, patient age and weight. The only variation that led to an ICER exceeding £30,000 vs BSC was a short time horizon (5 years, associated with an ICER of £34,140/QALY).

Similarly, the drivers of the comparison vs omalizumab included weight, relative rate of exacerbations in patients treated with omalizumab, and time horizon but the maximum ICER vs omalizumab was reported at £20,655/QALY.

Based on the PSA, reslizumab was identified as the optimal strategy in approximately 41.8% of cases at the £30,000 threshold to treat patients with severe eosinophilic asthma, who had experienced three prior exacerbations or more.

In the subgroup of patients with severe persistent IgE-mediated asthma, reslizumab was associated with a probability of 38.56% of being the optimal treatment strategy at the threshold of £30,000 per QALY compared to 7.19% for omalizumab.

The level of uncertainty was quite high in this analysis given the conservative distributions that were used to vary the parameters.

5.9 *Subgroup analysis*

5.9.1 *Methods*

Based on clinical experts' opinion and the expected treatment effect of reslizumab, subgroups were considered according to the number of exacerbations experienced in the year preceding treatment initiation.

As mentioned in Section 5.3.2, the model was calibrated to match the expected number of exacerbations in the BSC arm for each subgroup of interest: 2.32 in patients having experienced at least two exacerbations, 5.81 in patients in patients having experienced

at least four exacerbations, and 1.98 in adult patients classified as GINA 4/5. These estimates correspond to the mean number of exacerbations experienced by patients in the year preceding enrolment in the 3082 and 3083 trials.

The calibration was conducted by applying the multiplier for BSC to all transition probabilities of moving to the exacerbation health states for consistency purposes. This assumes that the selection of each subgroup affects the absolute rate of exacerbations in the BSC arm but not the relative treatment effect of reslizumab versus BSC. This assumption is conservative as analyses conducted by Teva UK Limited have shown that the relative treatment effect tended to be higher in subgroups of patients with higher rates of exacerbations.

5.9.2 *Results*

The results of the subgroup analyses are presented below.

Table 142: Subgroup analysis: Patients having experienced ≥2 exacerbations

Treatment arm	Total			Incremental			ICER/ QALY, £
	Costs, £	LYG	QALYs	Costs, £	LYG	QALYs	
BSC	[redacted]	[redacted]	[redacted]				
Reslizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,774

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 143: Subgroup analysis: Patients having experienced ≥4 exacerbations

Treatment arm	Total			Incremental			ICER/ QALY, £
	Costs, £	LY	QALYs	Costs, £	LYG	QALYs	
BSC	[redacted]	[redacted]	[redacted]				
Reslizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,006

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 144: Subgroup analysis: Adult patients (18+) classified as GINA Step 4/5

Treatment arm	Total			Incremental			ICER/ QALY, £
	Costs, £	LYG	QALYs	Costs, £	LYG	QALYs	
BSC	[redacted]	[redacted]	[redacted]				
Reslizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,738

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

5.9.3 *Subgroups excluded from the analysis*

Although patients on chronic OCS are of interest for this analysis, the reslizumab pivotal trials did not allow patients to decrease their dose of OCS, in order to not confound the relative treatment effect of reslizumab as an add-on therapy to BSC versus BSC. As a result, sufficient evidence is not available to quantify the impact of treating patients with reslizumab on the use of corticosteroids, and this subgroup could not be investigated further.

Similarly, sufficient evidence was not available to assess the cost-effectiveness of reslizumab in patients who do not adhere to treatment.

5.10 *Validation*

5.10.1 *Validation of de novo cost-effectiveness analysis*

One of the key assumptions of the model relates to the baseline risk of exacerbations, i.e. the fact that a common multiplier can be applied to all probabilities of transitioning to the exacerbation health states. The validity of this assumption was checked using two sets of transition probabilities: one generated based on all adult patients at GINA Steps 4 and 5 and one based on patients having experienced at least two exacerbations in the year preceding enrolment in the 3082 and 3083 trials.

The model was first run without any adjustment. Using the transition probabilities from the trials calculated based on this subgroup of patients, the mean rate of exacerbations in the BSC arm was 2.06 compared with 0.93 in the reslizumab arm. Reslizumab decreased the number of moderate and severe exacerbations by 50% and 53%, respectively.

The results in terms of clinical events are presented in Table 145.

Table 145. Transition probabilities based on patients having experienced 2≥ exacerbations in the 3082 and 3083 trials (multiplier=1): Clinical outcomes from the model

	Time controlled (years)	Time un-controlled (years)	# of moderate exacerbations	# of severe exacerbations	Deaths due to asthma	Exacerbation 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%

Using the transition probabilities based on all adult patients at GINA Steps 4 and 5, a multiplier of 1.535 was applied to match the annual rate of exacerbation of 2.06 in the BSC arm. The results based on this second approach are presented in Table 146.

Table 146. Transition probabilities based on all adults at GINA Step 4/5 in the 3082 and 3083 trials calibrated to simulate the subgroup of ≥2 exacerbations (multiplier=1.535): Clinical outcomes from the model

	Time controlled (years)	Time un-controlled (years)	# of moderate exacerbations	# of severe exacerbations	Deaths due to asthma	Exacerbation rate
Reslizumab (total)	18.56	13.12	6.32	26.73	0.17	0.97
On treatment	13.62	6.80	1.32	4.24	0.02	0.27
Off treatment	4.94	6.32	5.00	22.49	0.15	2.06
BSC	12.01	15.37	12.18	54.73	0.30	2.06
% difference	55%	-15%	-48%	-51%	-43%	-53%

As a consequence, the ICERs associated with these two scenarios were very similar: £50,878 for the first approach and £51,240 for the second approach.

In terms of validation with other publications, there is little relevant information available in order to make a comparison. The most relevant publication in this respect would have been included in the recent mepolizumab submission to NICE. Despite having access to the committee papers for this submission, the majority of results have been redacted in the report thus making a comparison extremely difficult.

Several of the studies captured in the economic evaluations SLR were used to validate the results of the current model. Faria et al (117) developed a decision analytic model of severe asthma from the perspective of the NHS. They reported total QALY values of 14.13 and 13.66 over a lifetime time horizon for omalizumab and BSC, respectively. The total QALY values reported in our base case results were 12.85 and 11.23 for omalizumab and BSC. Despite the fact that the analyses focused on different populations (Faria et al considered patients in GINA step 5 without any restriction on the baseline risk of exacerbations), the results produced by our model are in line with those published by Faria et al.

A second validation exercise was carried out during a comparison with Willson et al (118). This analysis focused on estimating the cost-effectiveness of tiotropium therapy as add-on to usual care in asthma patients who are uncontrolled despite treatment with ICS/LABA combination. The interventions are obviously not aligned, however a comparison was undertaken between the “usual care” treatment arm in Willson et al. and the “BSC” arm in the current analysis. As stated previously the number of total QALYs gained in our base case analysis was 11.23 for the BSC treatment arm. In the Willson study, the corresponding value is only slightly higher at 14.36.

Where possible, similar validation exercises were also carried out against papers captured in the cost and resource use SLR. In a study published in 2011, O’Neill et al (139) aimed to examine the costs of healthcare utilisation in a non-adherent group of patients with difficult-to-control asthma compared with adherent subjects. They reported both high and low estimates of total patient costs (excluding treatment regimen) of

£1,690.67 and £1,234.73, respectively. The corresponding figure derived from our model was £1,950 per year in the BSC treatment arm. When also considering that the analysis by O'Neill used NHS reference costs from 2006/2007, which will have increased over the previous 10 years, these figures are again in-line.

5.11 *Interpretation and conclusions of economic evidence*

No published studies were identified to address the NICE scope. The most relevant cost-effectiveness analysis is the mepolizumab NICE HTA submission; however the level of information available (drug costs not disclosed and results reported only as ICERs by subgroup) did not allow for a comparison of the results.

Although the label for reslizumab encompasses most adult patients at GINA Steps 4 and 5, the analyses presented as part of this submission focus on patients who have experienced at least three exacerbations in the year preceding treatment initiation. Based on clinical experts' advice, the expected treatment effect of reslizumab, and the fact that exacerbations are infrequent events that can vary from one year to the next, this population is believed to be the most appropriate group of patients to receive treatment on the NHS. The base case analysis was therefore based on patients who have experienced at least 3 exacerbations in the year preceding treatment initiation.

Costs and outcomes were estimated based on the most relevant sources for England and the model structure and parameters were validated with clinical experts to ensure relevance to England.

The main strength of the model is that it reflects the two dimensions of asthma: symptoms and exacerbations, based on a consistent common source for reslizumab and BSC (the reslizumab 3082 and 3083 trials). The main limitations are summarised below

- Given the fact that the target population in clinical practice will focus on patients with a history of exacerbations, the transition probabilities from the trial had to be adjusted accordingly through a multiplier applied across transition probabilities to an exacerbation health state
- Given the different indications of omalizumab and reslizumab and the lack of data for the intersection of the two populations, it proved difficult to accurately estimate the difference in treatment effect and disease progression.
- Given the lack of data related to moderate/severe/severe leading to hospital exacerbations and asthma-related deaths reported in the clinical trials, it was necessary to use secondary sources of information that were not always published.
- Health state costs are calculated by multiplying the unit costs of resources by the usage of that resource. This exercise was carried out by Willson et al (118) however it became apparent that the survey used to ascertain the resource usage values was conducted on a very limited sample size (n=15).
- The model imposes a discontinuation rule if a patient remains in the moderate/severe exacerbation or uncontrolled asthma health states for a year consecutively. This rule was validated by clinical experts and has direct

applicability to clinical practice. However due to the lack of long-term clinical data, we used the responder transition probabilities (16–52 weeks) as a proxy for those continuing treatment after 52 weeks.

- The waning of treatment effect was not explicitly included in the model. However, given that patients discontinue treatment after 12 months of being ‘not controlled’, this issue is partly accounted for.

6 Assessment of factors relevant to the NHS and other parties

6.1 *Population: people eligible for treatment*

In the base case scenario, which considers severe, uncontrolled asthma patients ≥18 years of age with elevated blood eosinophil levels (≥400 cells/µL), who have experienced 3 prior exacerbations in the past year (Table 147), the number of people eligible for reslizumab is estimated at [redacted] in Year 1, rising to [redacted] by Year 5. In an alternative scenario (scenario 1), which broadens the population to consider those patients who have experienced 2 prior exacerbations in the past year, the number of people eligible for reslizumab is estimated at [redacted] in Year 1, rising to [redacted] by Year 5 (Table 148). In another alternative scenario (scenario 2) with a narrower patient population (those who have experienced 4 prior exacerbations in the past year), the number of people eligible for reslizumab is estimated at [redacted] in Year 1, rising to [redacted] by Year 5 (Table 149).

Table 147: Estimation of patients eligible for treatment (base case)

	Year 1	Year 2	Year 3	Year 4	Year 5	Source
Population of England	54,786,300	55,186,240	55,589,100	55,994,900	56,403,663	ONS; population estimates for UK, 2015 (143) with 0.73% annual growth rate applied (144)
People ≥18 years	42,514,169	42,824,522	43,137,141	43,452,042	43,769,242	ONS; population estimates in England, 2015 (143)
People ≥18 years with asthma diagnosis	3,528,676	3,554,435	3,580,383	3,606,520	3,632,847	1 in 12 adults; Asthma UK (3)
People with severe asthma	352,868	355,444	358,038	360,652	363,285	10%; Peters et al, 2006 (145) Chung et al, 2014 (8)
People with elevated blood eosinophils	188,431	189,807	191,192	192,588	193,994	53.4%; Haughney et al, 2015 (30) Lee 2016 (31)
People with uncontrolled asthma	119,654	120,527	121,407	122,293	123,186	63.5%; Price et al, 2015 (14)
People experiencing 3 prior exacerbations in the past year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AAAAI, American Academy of Allergy, Asthma and Immunology; ONS, Office for National Statistics.

Table 148: Estimation of patients eligible for treatment (scenario 1)

	Year 1	Year 2	Year 3	Year 4	Year 5	Source

	Year 1	Year 2	Year 3	Year 4	Year 5	Source
Population of England	54,786,300	55,186,240	55,589,100	55,994,900	56,403,663	ONS; population estimates for UK, 2015 (143) with 0.73% annual growth rate applied (144)
People ≥18 years	42,514,169	42,824,522	43,137,141	43,452,042	43,769,242	ONS; population estimates in England, 2015 (143)
People ≥18 years with asthma diagnosis	3,528,676	3,554,435	3,580,383	3,606,520	3,632,847	1 in 12 adults; Asthma UK (3)
People with severe asthma	352,868	355,444	358,038	360,652	363,285	10%; Peters et al, 2006 (145) Chung et al, 2014 (8)
People with elevated blood eosinophils	188,431	189,807	191,192	192,588	193,994	53.4%; Haughney et al, 2015 (30) Lee 2016 (31)
People with uncontrolled asthma	119,654	120,527	121,407	122,293	123,186	63.5%; Price et al, 2015 (14)
People experiencing 2 prior exacerbations in the past year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ONS, Office for National Statistics.

Table 149: Estimation of patients eligible for treatment (scenario 2)

	Year 1	Year 2	Year 3	Year 4	Year 5	Source
Population of England	54,786,300	55,186,240	55,589,100	55,994,900	56,403,663	ONS; population estimates for UK, 2015 (143) with 0.73% annual growth rate applied (144)
People ≥18 years	42,514,169	42,824,522	43,137,141	43,452,042	43,769,242	ONS; population estimates in England, 2015 (143)
People ≥18 years with asthma diagnosis	3,528,676	3,554,435	3,580,383	3,606,520	3,632,847	1 in 12 adults; Asthma UK (3)
People with severe asthma	352,868	355,444	358,038	360,652	363,285	10%; Peters et al, 2006 (145) Chung et al, 2014 (8)
People with elevated blood eosinophils	188,431	189,807	191,192	192,588	193,994	53.4%; Haughney et al, 2015 (30) Lee 2016 (31)
People with	119,654	120,527	121,407	122,293	123,186	63.5%; Price et al,

	Year 1	Year 2	Year 3	Year 4	Year 5	Source
uncontrolled asthma						2015 (14)
People experiencing 4 prior exacerbations in the past year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ONS, Office for National Statistics.

6.2 *Costs included*

The tables below provide the estimated market shares and associated patient numbers following the introduction of reslizumab in the base case scenario, scenario 1 and scenario 2, respectively. The market shares are based on the following assumptions:

- Reslizumab-eligible patients are currently on BSC alone or add-on omalizumab.
- The market share for BSC alone decreases with the introduction of reslizumab.
- The market share for add-on omalizumab decreases with the introduction of reslizumab.
- The market share for eligible reslizumab patients comes from patients who would have otherwise received BSC alone or add-on omalizumab.
- Current market share of omalizumab represents omalizumab patients who would be eligible for add-on reslizumab (i.e. it does not reflect all patients currently on omalizumab).

Medicine costs used in the budget impact analysis are detailed in Table 118. The budget impact analysis does not consider any additional costs.

Table 150: Estimated market share and associated patient numbers with the introduction of reslizumab (base case)

	Year 1	Year 2	Year 3	Year 4	Year 5
Current scenario (without add-on reslizumab)					
BSC	24,582 (96.0%)	24,761 (96.0%)	24,942 (96.0%)	25,124 (96.0%)	25,307 (96.0%)
Add-on omalizumab	1,024 (4.0%)	1,032 (4.0%)	1,039 (4.0%)	1,047 (4.0%)	1,054 (4.0%)
Revised scenario (with introduction of add-on reslizumab)					
BSC	24,121 (94.2%)	23,833 (92.4%)	23,539 (90.6%)	23,240 (88.8%)	23,040 (87.4%)
Add-on omalizumab	973 (3.8%)	929 (3.6%)	883 (3.4%)	837 (3.2%)	791 (3.0%)
Add-on reslizumab	512 (2.0%)	1,032 (4.0%)	1,559 (6.0%)	2,094 (8.0%)	2,531 (9.6%)

Abbreviations: BSC, best standard of care.

Table 151: Estimated market share and associated patient numbers with the introduction of reslizumab (scenario 1)

	Year 1	Year 2	Year 3	Year 4	Year 5
Current scenario (without add-on reslizumab)					
BSC	48,614 (97.9%)	48,968 (97.9%)	49,326 (97.9%)	49,686 (97.9%)	50,049 (97.9%)
Add-on omalizumab	1,043 (2.1%)	1,050 (2.1%)	1,058 (2.1%)	1,066 (2.1%)	1,074 (2.1%)
Revised scenario (with introduction of add-on reslizumab)					
BSC	47,819 (96.3%)	47,368 (94.7%)	46,907 (93.1%)	46,438 (91.5%)	45,806 (89.6%)
Add-on omalizumab	993 (2.0%)	950 (1.9%)	907 (1.8%)	863 (1.7%)	818 (1.6%)
Add-on reslizumab	844 (1.7%)	1,701 (3.4%)	2,570 (5.1%)	3,451 (6.8%)	4,499 (8.8%)

Abbreviations: BSC, best standard of care.

Table 152: Estimated market share and associated patient numbers with the introduction of reslizumab (scenario 2)

	Year 1	Year 2	Year 3	Year 4	Year 5
Current scenario (without add-on reslizumab)					
BSC	14,193 (93.4%)	14,297 (93.4%)	14,401 (93.4%)	14,506 (93.4%)	14,612 (93.4%)
Add-on omalizumab	1,003 (6.6%)	1,010 (6.6%)	1,018 (6.6%)	1,025 (6.6%)	1,033 (6.6%)
Revised scenario (with introduction of add-on reslizumab)					
BSC	13,935 (91.7%)	13,792 (90.1%)	13,630 (88.4%)	13,466 (86.7%)	13,361 (85.4%)
Add-on omalizumab	957 (6.3%)	903 (5.9%)	863 (5.6%)	823 (5.3%)	782 (5.0%)
Add-on reslizumab	304 (2.0%)	612 (4.0%)	925 (6.0%)	1,243 (8.0%)	1,502 (9.6%)

Abbreviations: BSC, best standard of care.

6.3 *Resource savings*

The budget impact analysis does not include any estimates of resource savings.

6.4 *Budget impact*

Based on the submitted price for reslizumab, the budget impact of introducing reslizumab is estimated at [redacted] in Year 1, rising to [redacted] in Year 5 *[redacted] cumulative budget impact). Table 154 and Table 155 show the estimated budget impact in in scenarios 1 and 2, estimated at a cumulative budget impact of [redacted] and [redacted] over 5 years, respectively.

Table 153 shows the estimated budget impact to the NHS in England of introducing reslizumab, assuming positive NICE guidance in Teva's proposed patient population. Note that reslizumab is an add-on cost to BSC alone and a possible displacement cost versus omalizumab.

Based on the submitted price for reslizumab, the budget impact of introducing reslizumab is estimated at [redacted] in Year 1, rising to [redacted] in Year 5 [redacted] cumulative budget impact). Table 154 and Table 155 show the estimated budget impact in in scenarios 1 and 2, estimated at a cumulative budget impact of [redacted] and [redacted] over 5 years, respectively.

Table 153: Estimated budget impact of introducing add-on reslizumab (PAS price applied for reslizumab; base case)

	Year 1	Year 2	Year 3	Year 4	Year 5
Current scenario (without add-on reslizumab)					
BSC	£13,076,477	£13,171,935	£13,268,090	£13,364,947	£13,462,511
Add-on omalizumab	£5,848,628	£5,891,323	£5,934,330	£5,977,650	£6,021,287
Revised scenario (with introduction of add-on reslizumab)					
BSC	£12,831,293	£12,677,988	£12,521,760	£12,362,576	£12,256,495
Add-on omalizumab	£5,556,197	£5,302,191	£5,044,180	£4,782,120	£4,515,965
Add-on reslizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact					
BSC	-£245,184	-£493,948	-£746,330	-£1,002,371	-£1,206,017
Add-on omalizumab	-£292,431	-£589,132	-£890,149	-£1,195,530	-£1,505,322
Add-on reslizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Annual total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best standard of care.

Table 154: Estimated budget impact of introducing add-on reslizumab (PAS price applied for reslizumab) (scenario 1)

	Year 1	Year 2	Year 3	Year 4	Year 5
Current scenario (without add-on reslizumab)					
Total spending	£31,815,009	£32,047,259	£32,281,204	£32,516,856	£32,754,229
Revised scenario (with introduction of add-on reslizumab)					
Total spending	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact					
Annual total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 155: Estimated budget impact of introducing add-on reslizumab (PAS price applied for reslizumab) (scenario 2)

	Year 1	Year 2	Year 3	Year 4	Year 5
Current scenario (without add-on reslizumab)					
Total spending	£13,277,173	£13,374,096	£13,471,727	£13,570,071	£13,669,132
Revised scenario (with introduction of add-on reslizumab)					
Total spending	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact					
Annual total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.5 *Additional factors not included in analysis*

The introduction of reslizumab could be associated with additional resource savings, which were not included in the budget impact analysis. For example, in order to initiate treatment with omalizumab, patients are required to undergo testing for IgE levels, outside of routine testing, which incurs additional cost. Conversely, eosinophil levels – which are predicative of response with reslizumab – are tested using a simple blood test as part of the patient's routine assessment. Therefore, it is likely that introduction of reslizumab would reduce spending associated with treatment initiation.

The budget impact model also does not consider costs associated with the medicines included in the analysis – for example administration costs (specialist nurse time to administer the medicines) and monitoring costs (specialist nurse time to monitor patients post treatment administration). However, the impact of these costs on the results of the budget impact analysis will be negligible.

Finally, the model does not include the cost of managing exacerbations (systemic corticosteroid use, office visits, emergency department visits and hospitalisations). By reducing the number of clinically significant exacerbations compared with BSC, reslizumab could provide resource savings associated with treating exacerbations. However, for simplicity, savings associated with exacerbations are not included in this budget impact calculation.

6.6 *Limitations of the analysis*

There are several limitations of the budget impact analysis. Firstly, the model does not consider mortality (either general or asthma-specific). The indirect treatment comparison used to establish clinical outcomes used in the model does not take account of mortality rates between treatments. As such, no claims can be made about the comparative ability of treatments to prevent mortality.

Secondly, the market forecast does not take into account other IL-5 treatments that may be approved over the time horizon of the analysis. This is due to the current uncertainty surrounding approval of these treatments. If other treatments are approved in this class, the direct effect of the introduction of reslizumab on budgets will likely decrease.

Furthermore, costs associated with treatment-related AEs are not considered in the current analysis. However, while the management of such events associated with reslizumab will add to the budget impact, this increase will likely be offset by the cost of AEs associated with OCS, commonly prescribed to those receiving BSC.

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8 Appendices

Appendix 1: SmPC and EPAR

Appendix 1: Search strategy for relevant studies

Appendix 2: Quality assessment of RCTs

Appendix 3: Meta-analysis methodology

Appendix 4: Quality assessment of adverse reaction studies

Appendix 5: Search strategy for cost-effectiveness studies

Appendix 6: Quality assessment of cost-effectiveness studies

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Single technology appraisal

Reslizumab for treating asthma with elevated blood eosinophils inadequately controlled by inhaled corticosteroids [ID872]

Dear John,

The Evidence Review Group, Southampton Health Technology Assessments Centre, and the technical team at NICE have looked at the submission received on 14th July 2016 from Teva UK Limited. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **26th August 2016**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals: https://appraisals.nice.org.uk/request/16962

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Richard Diaz, Technical Lead (Richard.diaz@nice.org.uk). Any procedural questions should be addressed to Liv Gualda, Project Manager (liv.gualda@nice.org.uk).

Yours sincerely

Joanna Richardson
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Encl. checklist for confidential information

Section A: Clarification on effectiveness data

A1. Priority question: In sections 4.3 and 4.7 of the company submission, changes in outcomes from baseline are presented in the CS and CSRs in two ways: "change from baseline in ***over*** 16 (or 52) weeks" and "change from baseline ***to*** week 16 (or week 52)".

- Please clarify what these terms mean and whether they are synonymous.

The ERG understands that one set of change-from-baseline analyses used a mixed effect model for repeated measures (MMRM) and another set of change-from-baseline analyses used an analysis of covariance (ANCOVA) model.

- Do these two approaches to the analyses correspond to the two ways that changes from baseline are phrased?

- Please clarify which analysis method was employed for each of the changes from baseline reported in section 4.7 of the CS.

A2. Priority question: Figure 35 on page 127 of the company submission is a CONSORT diagram for C38072/3084. This diagram does not account for 15 randomised patients who were excluded from analyses (as stated on page 19 of the study 3084 clinical study report).

- Please provide an updated flow chart or explanation.

There is a footnote (a) in the box labelled "Patients enrolled/randomised" which is not included at the bottom of the figure.

- Please clarify what footnote (a) should state.

A3. Priority question: In section 4.9 of the company's submission, the rationale for deciding which outcomes were included in the meta-analyses are not explained. Although the company submission refers the reader to Appendix 4 for this information, it does not appear to have been provided.

- Please explain why PEFR, % predicted FEV_1, FVC, and $FEF_{25-75\%}$ were not included in meta-analyses.

- Furthermore, the list of outcomes in Appendix 4 seems incomplete (for example, it is missing PEFR and $FEF_{25-75\%}$).

A4. Table 9 on page 39 in the company's submission summarises the stepwise approach to asthma treatment recommended by the Global Initiative for Asthma (GINA). Patients at step 4 and 5 correspond to the patients in the trials and the model. The GINA approach recommends that at steps 4 and 5, add-on therapy with tiotropium bromide should be considered. Please clarify whether the pivotal trials (3082 and 3083) include treatment with

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tiotropium bromide in the placebo comparator arm. Please clarify which treatments patients in the placebo arms of the pivotal trials were allowed to take as part of standard care, and what proportion of patients received these treatments.

A5. Page 45 of the company's submission: In reference to the title and abstract screening having been reviewed by two analysts, please explain what "one in charge of the primary screening and the second one responsible for the quality check" means? Please clarify whether the second reviewer followed the pre-specified eligibility criteria or performed another type of quality assessment. If the latter is true, please explain the rationale for not following the pre-specified eligibility criteria during the quality check stage of title and abstract screening?

A6. On page 46 of the company submission, it states that 21 publications met the inclusion criteria. The five reslizumab RCTs are cited in table 12 of the company submission, but the remaining 16 RCTs which provide evidence for omalizumab (numbers 79 to 94 in the company submission references) have not been included in a similar table. Please provide a table similar to table 12 of the company submission describing the 16 omalizumab RCTs including publications and sources for these references.

A7. In the schematic for the systematic review of clinical evidence (figure 1 on page 46 of the company submission), it describes at the identification stage that an additional 213 publications and sources had been identified in addition to those publications identified through database searching. Please provide details of those additional 213 publications and sources.

A8. The 191 studies excluded from the systematic review are listed in the appendix to the company's submission, in table 5 in section 2.3. Although the author, title and year of publication is included, the journal details or conference abstract details are not included. Please provide the journal details for each publication or if an abstract at which conference it was presented, including those reported as being unable to retrieve.

A9. In table 12 on page 48 of the company's submission, the reason for excluding the RCT Res-5-0010 reported does not seem to concur with the inclusion/exclusion criteria. Please explain clearly whether this study met the pre-specified eligibility criteria or not:

- if Res-5-0010 meets the inclusion criteria for the systematic review, please provide a quality assessment for that trial.

- if Res-5-0010 does not meet the inclusion criteria, please explain why it was then included in the direct meta-analyses and indirect treatment comparisons.

- if Res-5-0010 does not meet the inclusion criteria, please provide results for the relevant direct meta-analyses and indirect treatment comparisons with Res-5-0010 excluded.

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A10. Please explain the rationale and describe the method for the sensitivity analysis titled "Analysis using an offset variable that did not exclude the summed duration of clinical asthma exacerbations (CAEs) from the follow-up time" referred to in table 16 on page 62 of the company submission.

A11. In Appendix 3 of the company submission, for studies 3082, 3083, 3081, and 3084 the quality assessment question about adequacy of allocation concealment has not been answered. The ERG understands from each of the CSRs that the randomisation code was concealed, but since blinding and allocation concealment are different processes, please clarify how the randomisation code was used to allocate the patients to the trial arms and how this part of the process was concealed from study personnel?

A12. In section 4.9.2 on page 139 and the indirect treatment comparison (Amaris report) the outcomes in the direct and indirect meta-analyses are reported imprecisely as time points ±4 weeks. Please clarify the reason for this. Three of the included RCTs reported outcomes at 4-weekly intervals, meaning that there is potential for confusion as to whether the 16±4 week time point includes data from 12, 16 and/or 20 weeks; and as to whether the 52 week time point includes data from 48 and/or 52 weeks.

A13. With regard to section 4.14 on page 176, please provide a list of relevant ongoing studies for reslizumab in patients with asthma and elevated blood eosinophils, regardless of the evidence being available in the next 12 months.

A14. The questions below relate to the *Amaris ITC report*.

- Please could you clarify if the second analyst for the screening of titles and abstracts conducted a full 'quality' check of all the primary screening or a percentage check?

- What was the screening procedure for full text publications? (for example, how many reviewers were involved)

- Please provide the WinBUGS code used for the indirect treatment comparison.

- In table 7 of the ITC on page 35, only 17 studies are mentioned instead of 21. Does this mean 4 studies did not provide a definition of exacerbations? Unlike in the other tables of the Amaris report, there are no ticks in this table, only crosses. Do the crosses indicate that the definition is provided in a study or that all definitions are provided unless crossed?

- Please explain why the study by Castro et al. 2011 (RES-5-0010) is omitted from table 8 on page 38 of the Amaris Report when it appears in Table 9?

- Please explain the discrepancy in the number of studies listed per feasible endpoint between table 34 on page 55 and table 84 in Appendix 4.

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- The text under table 37 on page 59 states that a positive change from baseline indicates that reslizumab is more effective than omalizumab for FEV1 at 16 weeks, but table 39 on page 60 states the opposite. Please provide an explanation for this discrepancy.

Section B: Clarification on cost-effectiveness data

B1. Priority question: In sections 5.2.2 and 5.3.2.2 of the submission, it is indicated that "the algorithm" is used to calculate transition probabilities for weeks 0-16, weeks 16-52 and post-52 weeks. However, only the results of the algorithm were presented.

- Please provide the full calculations necessary for determining transition probabilities and the assumptions for these calculations in an Excel spreadsheet.

- In a similar way please provide these details for calculating the proportion of non-responders.

B2. In table 117 of the company submission, it is unclear how the cost of a severe exacerbation-related hospitalisation was calculated. It is indicated that weighted average costs from the healthcare resource group (HRG codes DZ15M, DZ15N, and DZ15P are used. However, the schedules (non-elective short stay [NES], non-elective long stay [NEL], day cases [DC]) that are averaged are not provided, therefore the ERG are unable to calculate these costs. Please provide the full cost calculations for HRG codes DZ15M/N/P with clear referencing to which schedules were used.

B3. The ERG was unable to identify HRG code DA15QR which is referenced in table 117, page 206 of the company's submission. Please indicate the source of this code or supply a corrected code.

B4. In table 121, page 212 of the submission, costs derived from table 120 on the previous page are synthesised into aggregate values for each health state. The ERG tried synthesising the costs to reproduce table 121, but were unable to do so. Please explain the discrepancy between the two tables and please provide an Excel spreadsheet with calculations for health state costs in the model.

B5. Table 138 on page 236 of the company submission provides the results of a scenario analysis using utility data mapped from the Asthma Quality of Life Questionnaire (AQLQ) using an algorithm by Tsuchiya and colleagues. Please provide complete details of the data used for mapping, including: how patients were matched to the health states, the AQLQ values that correspond to these health states, and the mapped EQ-5D values that correspond to these health states.

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B6. Please describe what changes need to be made to the economic model to produce the subgroup analyses for adult patients classified as GINA step 4/5 in table 144 on page 238 of the company's submission.

B7. In the estimation of the transition probabilities, the company used the actual transition between health states from the two pivotal trials. However, the number of patients in each health state as stated in table 102 on page 186 does not match the number of patients in the model worksheet named "Sheet1" in the economic model. Please explain the differences in these numbers?

B8. On page 239, the company states that a multiplier of 1.535 was applied to match the annual rate of exacerbation of 2.06 in the BSC arm, using the transition probabilities based on all adult patients at GINA Steps 4 and 5. Please clarify how the multiplier used to estimate the risk of exacerbations has been calculated.

Section C: Textual clarifications and additional points

C1. As the Teva treatment algorithm is yet to be published, it is therefore marked as academic in confidence. However, for a treatment algorithm to effectively address the unmet need, it should be made publicly available to the specialists who would use it. Is there a known publication date for the treatment algorithm? Has the treatment algorithm been endorsed by any asthma specialists?

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Friday 26th August 2016

Dear Joanne Richardson,

Thank you for the opportunity to respond to the clarification questions posed by the Evidence Review Group, Southampton Health Technology Assessments Centre, and the technical team at NICE regarding the Teva UK Limited submission for reslizumab [ID872]. Please find below responses to the clarification questions along with the following accompanying documents (please note Appendix 2, 3 and 4 are classed as Commercial in Confidence):

Microsoft Excel file:

Appendix_1_SLR_details of additional and excluded publications.xlsx

Microsoft Excel file:

Appendix_2_Transition_Matrices_CIC.xlsx

Microsoft Excel file:

Appendix_3_Health state-specific cost calculations_CIC.xlsx

While reviewing the company submission during the preparation of these responses, Teva identified two inconsistencies in the economic model that was sent to NICE as part of the original company submission. For transparency and completion, Teva would like to bring these inconsistencies to NICE's attention by sending the following document with this response letter:

Appendix_4_Model_document_CIC.docx

Teva can provide an updated economic model (Excel file) that rectifies these two identified inconsistencies at the request of NICE.

If you require any further information please let me know.

Kind regards,

John Holmes

Head of Medical Affairs

Teva UK Limited

Abbreviations

ACQ	Asthma Control Questionnaire
ANCOVA	Analysis of covariance
AQLQ	Asthma Quality of Life Questionnaire
BOCF	Baseline observation carried forward
BSC	Best standard of care
CAE	Clinical asthma exacerbation
CSC	Clinical Supply Chain
EQ-5D	EuroQol 5-dimensions questionnaire
FDA	US Food and Drug Administration
$FEF_{25–75\%}$	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
ICS	Inhaled corticosteroid
IRT	Interactive Response Technology
ITC	Indirect treatment comparison
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive voice response system
LABA	Long-acting beta-agonist
LOCF	Last observation carried forward
MMRM	Mixed-effect model for repeated measures
OCS	Oral corticosteroid
PD	Pharmacodynamic
PEFR	Peak expiratory flow rate
PK	Pharmacokinetic
RCT	Randomised controlled trial
SABA	Short-acting beta-agonist
SLR	Systematic literature review

1. Section A: Clarification on effectiveness data

A1. Priority question: In sections 4.3 and 4.7 of the company submission, changes in outcomes from baseline are presented in the CS and CSRs in two ways: "change from baseline in *over* 16 (or 52) weeks" and "change from baseline *to* week 16 (or week 52)".

- **Please clarify what these terms mean and whether they are synonymous.**

The ERG understands that one set of change-from-baseline analyses used a mixed effect model for repeated measures (MMRM) and another set of change-from-baseline analyses used an analysis of covariance (ANCOVA) model.

- **Do these two approaches to the analyses correspond to the two ways that changes from baseline are phrased?**

- **Please clarify which analysis method was employed for each of the changes from baseline reported in section 4.7 of the CS.**

Both change from baseline over 16 (or 52) weeks and change from baseline to Week 16 (or Week 52) are outputs from the same MMRM model (not ANCOVA). Over 16 (or 52) weeks" can be viewed as the weighted average across the entire 52-week period. To Week 16 (or Week 52) is the estimate for that specific timepoint at Week 16 (or Week 52). The same MMRM model was employed for each of the changes from baseline reported in Section 4.7 of the company submission.

A2. Priority question: Figure 35 on page 127 of the company submission is a CONSORT diagram for C38072/3084. This diagram does not account for 15 randomised patients who were excluded from analyses (as stated on page 19 of the study 3084 clinical study report).

- **Please provide an updated flow chart or explanation.**

As detailed in the response to the question below, a footnote to clarify this point should have been included at the bottom of Figure 35 in the company submission. The 15 randomised patients not accounted for in the CONSORT diagram for Study 3084 were from sites [redacted], for which study participation was terminated for the following reasons:

- Site [redacted] was terminated due to numerous, unresolved Good Clinical Practice issues, suspicious data, and potential safety risks to patients being enrolled (letter to the US Food and Drug Administration [FDA] dated 14 August 2013).
- Site [redacted] was terminated due to an Acquisition/Petition to Revoke filed with the Medical Board of California (letter to FDA dated 5 June 2013).

The data from these two sites were thus deemed invalid and patient data were excluded from all analyses.

There is a footnote (a) in the box labelled "Patients enrolled/randomised" which is not included at the bottom of the figure.

- **Please clarify what footnote (a) should state.**

Footnote (a) should state:

This number does not include 15 randomly assigned patients from study sites whose participation in the study was terminated for procedural violations and an additional patient who was randomised in error and subsequently lost to follow-up.

A3. Priority question: In section 4.9 of the company's submission, the rationale for deciding which outcomes were included in the meta-analyses are not explained. Although the company submission refers the reader to Appendix 4 for this information, it does not appear to have been provided.

- **Please explain why PEFR, % predicted FEV_1, FVC, and $FEF_{25-75\%}$ were not included in meta-analyses.**

The final scope issued by NICE listed the following outcome measures to be considered: asthma control, incidence of clinically significant exacerbations, including those with required unscheduled contact with healthcare professionals or hospitalisation, use of oral corticosteroids, patient and clinician evaluation of response, lung function, mortality, time to discontinuation, adverse effects of treatment, and health-related quality of life. Endpoint measures for each of these outcomes were defined based on clinical expert opinion and based on the endpoints included in the reslizumab trials. Endpoint selection for the meta-analyses was based on the number of studies from which data were available. In other words, endpoints with the highest number of studies reporting data for specific endpoints of interest were preferred. For this reason, the analysis focused on forced expiratory volume in one second (FEV_1) rather than % predicted FEV_1 and forced vital capacity (FVC).

- **Furthermore, the list of outcomes in Appendix 4 seems incomplete (for example, it is missing PEFR and $FEF_{25-75\%}$).**

All outcomes listed in the scope (see first part of answer to question A3) were considered. Peak expiratory flow rate (PEFR) and forced expiratory flow at 25–75% forced vital capacity ($FEF_{25-75\%}$) were not considered to be endpoints of interest for the outcome of asthma control due to limited information reported in the literature and, consequently, the lack of added value of estimating the relative efficacy of reslizumab for the cost-effectiveness model.

A4. Table 9 on page 39 in the company's submission summarises the stepwise approach to asthma treatment recommended by the Global Initiative for Asthma (GINA). Patients at step 4 and 5 correspond to the patients in the trials and the model. The GINA approach recommends that at steps 4 and 5, add-on therapy with tiotropium bromide should be considered.

- **Please clarify whether the pivotal trials (3082 and 3083) include treatment with tiotropium bromide in the placebo comparator arm.**

A small proportion (5–6%) of patients in the reslizumab and placebo arms of both Study 3082 and Study 3083 were receiving tiotropium bromide at baseline. During the 52-week treatment period, 5% and 4% of patients in the placebo arm of Study 3082 and Study 3083, respectively, received tiotropium bromide.

- **Please clarify which treatments patients in the placebo arms of the pivotal trials were allowed to take as part of standard care, and what proportion of patients received these treatments.**

In studies 3082 and 3083, patients' baseline asthma therapy had to include at least 440 µg of inhaled fluticasone daily (or equivalent). Baseline asthma therapy could also include the following medications, provided that they had been stable for 30 days prior to screening and continued without dosage changes throughout the study:

- Long-acting beta-agonists (LABA)
- Inhaled corticosteroids (ICS)
- Oral corticosteroids (OCS; ≤10 mg prednisone daily or equivalent)
- Leukotriene antagonists
- 5-lipoxygenase inhibitors
- Cromolyn sodium

Use of asthma medications prior to the baseline visit in the drugs for obstructive airway disease and corticosteroids for systemic use therapeutic classes is presented in Table 1.

Use of asthma medications during the 52-week period for obstructive airway disease and corticosteroids for systemic use therapeutic classes is presented in Table 2 and Table 3.

As detailed in Table 13 of the company submission, prohibited medications were anti-human IL-5 monoclonal antibodies, including reslizumab, mepolizumab and benralizumab. The following medications were restricted prior to baseline (with corresponding washout times):

- Systemic corticosteroids (30-day washout; as detailed above OCS ≤10 mg prednisone daily or equivalent were allowed if the dosage was stable for 30 days prior to screening and was unchanged throughout the study)
- Any immunosuppressive or immunomodulatory agents, including, but not limited to, methotrexate, cyclosporin, and interferon-α (6-month washout)
- Anti-TNF monoclonal antibody (6-month washout)
- All other non-biologic investigational drugs (30-day washout)
- Live attenuated vaccines (12-week washout)
- All other biologic therapies, including omalizumab (6-month washout)

Patients were to refrain from using short-acting beta-agonists (SABAs) for 6 hours, and LABAs for 12 hours, prior to any study visit that included spirometry or airway reversibility testing, including the screening visit.

In Study 3082, 99% (483 out of 489) of patients were receiving at least one asthma medication prior to baseline. Almost all (≥98%) used prior medications in the drugs for obstructive airway disease therapeutic class. The second most common therapeutic class was corticosteroids for systemic use (11% of patients in the reslizumab group and 17% in the placebo group). No more than 1% of all patients used prior asthma medications from other therapeutic classes.

Similarly, >99% (463/464) of patients in Study 3083 received at least one asthma medication prior to the baseline visit. Medications in the drugs for obstructive airway disease therapeutic class were used by >99% of patients. Corticosteroids for systemic use were used by 11% and 9% of patients in the reslizumab and placebo groups, respectively. Antihistamines for systemic use, and cough and cold preparations were taken by 2% of all patients; otherwise no more than 1% of all patients used prior asthma medications from other therapeutic classes.

Table 1: Studies 3082 and 3083 – prior asthma medications (drugs for obstructive airway diseases and corticosteroids for systemic use therapeutic classes) in the placebo arm – randomised set

Therapeutic class **Drug class** Generic term[†]	**Study 3082, number (%) of patients** **Placebo** **N=244**	**Study 3083, number (%) of patients** **Placebo** **N=232**
Drugs for obstructive airway disease	**242 (>99)**	**231 (>99)**
Short-acting inhaled bronchodilators (including short-acting combinations)	**207 (85)**	**210 (91)**
Albuterol	186 (76)	188 (81)
Ipratropium and fenoterol	13 (5)	9 (4)
Ipratropium	11 (5)	8 (3)
Terbutaline	7 (3)	7 (3)
Fenoterol	6 (2)	10 (4)
Ipratropium and albuterol	2 (<1)	1 (<1)
Inhaled corticosteroids and long-acting β_2-agonists	**173 (71)**	**142 (61)**
Salmeterol and fluticasone	103 (42)	91 (39)
Budesonide and formoterol	63 (26)	39 (17)
Beclomethasone and formoterol	9 (4)	12 (5)
Mometasone and formoterol	5 (2)	0
Inhaled corticosteroids	**87 (36)**	**93 (40)**
Fluticasone	26 (11)	38 (16)
Budesonide	22 (9)	27 (12)
Ciclesonide	20 (8)	10 (4)
Beclomethasone	19 (8)	28 (12)
Mometasone	1 (<1)	1 (<1)

Therapeutic class **Drug class** Generic term[†]	**Study 3082, number (%) of patients** **Placebo** **N=244**	**Study 3083, number (%) of patients** **Placebo** **N=232**
Leukotriene inhibitors	**65 (27)**	**43 (19)**
Montelukast	63 (26)	33 (14)
Zafirlukast	2 (<1)	1 (<1)
Zileuton	0	0
Pranlukast	0	9 (4)
Long-acting β_2-agonists	**37 (15)**	**54 (23)**
Formoterol	20 (8)	30 (13)
Salmeterol	16 (7)	24 (10)
Indacaterol	1 (<1)	0
Xanthine derivative bronchodilators	**28 (11)**	**16 (7)**
Theophylline	28 (11)	16 (7)
Aminophylline	0	0
Doxophylline	0	0
Long-acting muscarinic receptor antagonists	**15 (6)**	**11 (5)**
Tiotropium	15 (6)	11 (5)
Chromone	**3 (1)**	0
Cromoglicate	3 (1)	0
Recombinant humanized anti-IgE monoclonal antibody	**3 (1)**	**5 (2)**
Omalizumab	3 (1)	5 (2)
Oral bronchodilator	**0**	**2 (<1)**

Therapeutic class **Drug class** Generic term[†]	**Study 3082, number (%) of patients** **Placebo** **N=244**	**Study 3083, number (%) of patients** **Placebo** **N=232**
Procaterol	0	2 (<1)
Corticosteroids for systemic use	**42 (17)**	**20 (9)**
Prednisone	17 (7)	8 (3)
Methylprednisolone	17 (7)	2 (<1)
Prednisolone	6 (2)	9 (4)
Dexamethasone	2 (<1)	0
Betamethasone	0	0
Prednisolone acetate	0	1 (<1)
Triamcinolone	0	0

[†]All medications were indicated for asthma in the electronic case report form.

Patients are counted only once for each generic term and in each therapeutic class. Inhaled corticosteroids were a requisite background medication in all patients. The groups receiving an inhaled corticosteroid at baseline or an inhaled corticosteroid and long-acting beta-agonist at baseline were not mutually exclusive, resulting in a total incidence of use of all inhaled corticosteroids that exceeds 100%.

Table 2: Study 3082 – asthma medications in the placebo arm in the 52-week treatment period

Drug class Generic term	**Placebo arm (N=244);** **number (%) of patients**
Long-acting muscarinic receptor antagonists	
Tiotropium bromide	12 (5)
Long-acting β_2-agonists and inhaled corticosteroids	
Salmeterol and fluticasone	101 (41)
Budesonide and formoterol	63 (26)
Beclomethasone and formoterol	9 (4)
Mometasone and formoterol	5 (2)
Inhaled corticosteroids	
Fluticasone	23 (9)
Beclomethasone	18 (7)
Budesonide	21 (9)
Ciclesonide	20 (8)
Mometasone	1 (<1)
Long-acting β_2-agonists	
Formoterol	19 (8)
Salmeterol	15 (6)
Leukotriene inhibitors	
Montelukast	63 (26)
Zafirlukast	2 (<1)
Xanthine-derivative bronchodilators	
Theophylline	27 (11)

Table 3: Study 3083 – asthma medications in the placebo arm in the 52-week treatment period

Drug class Generic term	**Placebo arm (N=232);** **number (%) of patients**
Long-acting muscarinic receptor antagonists	
Tiotropium bromide	10 (4)
Long-acting β_2-agonists and inhaled corticosteroids	
Salmeterol and fluticasone	92 (40)
Budesonide and formoterol	40 (17)
Beclomethasone and formoterol	11 (5)
Inhaled corticosteroids	
Fluticasone	37 (16)
Beclomethasone	28 (12)
Budesonide	24 (10)

Drug class Generic term	**Placebo arm (N=232);** **number (%) of patients**
Ciclesonide	10 (4)
Mometasone	2 (<1)
Long-acting β_2-agonists	
Formoterol	30 (13)
Salmeterol	23 (10)
Leukotriene inhibitors	
Montelukast	32 (14)
Pranlukast	9 (4)
Zafirlukast	1 (<1)
Xanthine-derivative bronchodilators	
Theophylline	16 (7)
Oral bronchodilator	
Procaterol	2 (<1)

A5. Page 45 of the company's submission: In reference to the title and abstract screening having been reviewed by two analysts, please explain what "one in charge of the primary screening and the second one responsible for the quality check" means? Please clarify whether the second reviewer followed the pre-specified eligibility criteria or performed another type of quality assessment. If the latter is true, please explain the rationale for not following the pre-specified eligibility criteria during the quality check stage of title and abstract screening?

During the quality check stage of title and abstract screening, the second reviewer followed the pre-specified eligibility criteria in order to ensure the quality of the screening at that stage of the systematic literature review (SLR) process. Discrepancies between reviewers were resolved through consultation with a neutral third party.

A6. On page 46 of the company submission, it states that 21 publications met the inclusion criteria. The five reslizumab RCTs are cited in table 12 of the company submission, but the remaining 16 RCTs which provide evidence for omalizumab (numbers 79 to 94 in the company submission references) have not been included in a similar table. Please provide a table similar to table 12 of the company submission describing the 16 omalizumab RCTs including publications and sources for these references.

Details of the 16 RCTs identified in the SLR that provide evidence for omalizumab are provided in Table 4.

Table 4: RCTs that provide evidence for omalizumab

Trial name/ publication	Population	Intervention	Comparator	Reference
Garcia et al, 2013	Adult patients with severe, difficult to control, nonatopic asthma	Omalizumab	Placebo/BSC	(1)
Busse et al, 2001	Patients aged 12–75 years with severe allergic asthma	Omalizumab	Placebo/BSC	(2)
Chanez et al, 2010	Adult patients with severe allergic asthma	Omalizumab	Placebo/BSC	(3)
EXTRA	Patients aged 12–75 years with severe allergic asthma	Omalizumab	Placebo/BSC	Hanania, 2011 (4)
Holgate et al, 2004	Patients aged 12–75 years with severe allergic asthma	Omalizumab	Placebo/BSC	(5)
Ayres et al, 2004	Patients aged 12–75 years with persistent (>2 years), moderate-to-severe, allergic asthma	Omalizumab	Placebo/BSC	(6)
Ohta et al, 2009	Patients aged 20–75 years with moderate-to-severe persistent asthma	Omalizumab	Placebo/BSC	(7)
SOLAR	Patients aged 12–75 years with moderate-to-severe allergic asthma and persistent allergic rhinitis	Omalizumab	Placebo/BSC	Vignola, 2004 (8)
INNOVATE	Patients aged 12–75 years with severe persistent asthma	Omalizumab	Placebo/BSC	Humbert, 2005 (9)
Soler et al, 2001	Patients aged 12–75 years with moderate-to-severe allergic asthma	Omalizumab	Placebo/BSC	(10)
Buhl et al, 2002	Patients aged 12–75 years with moderate-to-severe allergic asthma	Omalizumab	Placebo/BSC	(11)
Niven et al, 2008	(population as in Ayres et al, 2004)	Omalizumab	Placebo/BSC	Post-hoc analysis of Ayres et al, 2004[†] (12)
EXALT	Patients aged 12–75 years with severe allergic asthma	Omalizumab	Placebo/BSC	Bousquet, 2011 (13)
Hoshino et al, 2012	Patients aged 20–75 years with severe allergic asthma	Omalizumab	Placebo/BSC	(14)
QUALITX	Patients aged 12–75 years with severe allergic asthma	Omalizumab	Placebo/BSC	Rubin et al, 2012 (15)
Siergiejko et al, 2011	(population as in the EXALT study)	Omalizumab	Placebo/BSC	Post-hoc analysis of EXALT[†] (16)

Abbreviations: BSC, best standard of care; RCT, randomised controlled trial. [†]Reports complimentary results.

A7. In the schematic for the systematic review of clinical evidence (figure 1 on page 46 of the company submission), it describes at the identification stage that an additional 213 publications and sources had been identified in addition to those publications identified through database searching. Please provide details of those additional 213 publications and sources.

The list of additional database searches conducted as part of the hand searches pre-specified in the SLR protocol is provided in the Excel file sent to NICE with this response letter (file name: *Appendix_1_SLR_details of additional and excluded publications.xlsx*). The source and website URL is provided for each record, as well as the number of hits retrieved and screened. The total number of hits was 213.

A8. The 191 studies excluded from the systematic review are listed in the appendix to the company's submission, in table 5 in section 2.3. Although the author, title and year of publication is included, the journal details or conference abstract details are not included. Please provide the journal details for each publication or if an abstract at which conference it was presented, including those reported as being unable to retrieve.

Please refer to the Excel file sent with this response letter (file name: *Appendix_1_SLR_details of additional and excluded publications.xlsx*) for further details of the 191 studies excluded from the SLR. Journal or conference abstract details have been added where available.

A9. In table 12 on page 48 of the company's submission, the reason for excluding the RCT Res-5-0010 reported does not seem to concur with the inclusion/exclusion criteria. Please explain clearly whether this study met the pre-specified eligibility criteria or not:

- **if Res-5-0010 meets the inclusion criteria for the systematic review, please provide a quality assessment for that trial.**
- **if Res-5-0010 does not meet the inclusion criteria, please explain why it was then included in the direct meta-analyses and indirect treatment comparisons.**
- **if Res-5-0010 does not meet the inclusion criteria, please provide results for the relevant direct meta-analyses and indirect treatment comparisons with Res-5-0010 excluded.**

Res-5-0010 met the inclusion criteria for the SLR and was one of the 21 included studies. However, this trial was not presented in the company submission as it was a small (N=106), Phase II, proof of concept study that informed the Phase III programme). A quality assessment for Res-5-0010 (17, 18) is provided in Table 5.

Table 5: Quality assessment for Res-5-0010

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/NA)
Was randomisation carried out appropriately?	Patients were randomised in a 1:1 ratio to reslizumab 3.0 mg/kg or	Yes

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/NA)
	placebo using a central IVRS which used computerised randomisation. Patients were stratified at randomisation by baseline ACQ score (≤2 or >2)	
Was the concealment of treatment allocation adequate?	Patients were randomly assigned to treatment using an IVRS that used computerised randomisation. At baseline, the study site personnel obtained via IVRS the patient study number and the corresponding study drug assignment from a computer-generated randomisation code. The IVRS referenced the randomisation code and assigned a treatment for each eligible patient. At each study site, the study pharmacist (or designee) was unblinded and prepared study drug for administration according to the randomisation code provided by the IVRS. With the exception of the unblinded study pharmacist (or designee), the randomisation code was not disclosed to the investigator or any other study personnel involved in the conduct of the study, unless in the case of an emergency Study drug (reslizumab or placebo) was administered in a double-blind manner. The sponsor, investigator, other study site staff, and subject were blinded to the randomisation schedule during the treatment phase of the study. The primary clinical research associate (CRA) was also blinded to the randomisation schedule. An unblinded study monitor performed study drug accountability. The Sponsor had access to unblinded data after database lock. Doses of reslizumab and placebo were administered in the same total volume for subjects of the same weight in order to maintain the study blind.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Yes. Patient baseline demographics and disease-specific characteristics were well balanced between the reslizumab and placebo groups.	Yes
Were the care providers, participants and outcome assessors blind to	Patients, investigators, the primary clinical research associate, and other study site staff were blinded to	Yes

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/NA)
treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	the randomisation schedule. The sponsor was granted access to unblinded data after database lock. The study pharmacist (or designee) at each site was unblinded and prepared study drugs (reslizumab or placebo) for administration according to the randomization code provided by the IVRS.	
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	In total, 6% of patients in the reslizumab group withdrew (4% due to lack of efficacy/worsening of disease and 2% due to lack of interest in continuing visits) compared with 17% of patients in the placebo group (15% due to lack of efficacy/worsening of disease; 2% due to adverse events).	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All treatment outcomes were reported in the CSR except for the following exploratory variable: Nasal mucus eosinophil levels – too few samples were obtained to perform an analysis.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	All randomised subjects who received any amount of study drug were included in the ITT analysis set; this analysis set was used for the efficacy and safety analyses. For the primary efficacy analysis (ITT analysis set), subjects with a missing ACQ score at end-of-trial were treated using two approaches: LOCF as the primary analysis, and the BOCF as the sensitivity analysis. Subjects who require systemic corticosteroids (including OCS) were treated as dropouts and subsequent ACQ scores were considered as missing and imputed according to the above procedure for the ITT analysis of efficacy. No missing data imputation was applied for any other efficacy analyses.	Yes

Abbreviations: ACQ, asthma control questionnaire; BOCF, baseline observation carried forward; ITT, intent-to-treat; IVRS, interactive voice response system; LOCF, last observation carried forward; OCS, oral corticosteroid.

A10. Please explain the rationale and describe the method for the sensitivity analysis titled "Analysis using an offset variable that did not exclude the summed duration of

clinical asthma exacerbations (CAEs) from the follow-up time" referred to in table 16 on page 62 of the company submission.

In studies 3082 and 3083, primary analysis of the frequency of CAEs during the 52-week treatment period used the negative binomial model that included the treatment group and randomisation stratification factors as model factors and the logarithm of follow-up time excluding the summed duration of CAE events as an offset variable. This offset variable adjusted the CAE rate for the total duration of patient exposure to study drug when not experiencing a CAE. The primary analysis was repeated in a sensitivity analysis using an offset that did not exclude the summed duration of exacerbations from the follow-up time in the offset calculation.

Results of this sensitivity analysis were similar to the results using the primary model in both 3082 and 3083. Hence, a reslizumab treatment effect is still obtained without excluding the summed duration of CAEs from drug exposure – i.e. the results of the primary efficacy analysis were not affected by subtracting the summed duration of exacerbations from the follow-up period in the calculation of the offset of the negative binomial model.

A11. In Appendix 3 of the company submission, for studies 3082, 3083, 3081, and 3084 the quality assessment question about adequacy of allocation concealment has not been answered. The ERG understands from each of the CSRs that the randomisation code was concealed, but since blinding and allocation concealment are different processes, please clarify how the randomisation code was used to allocate the patients to the trial arms and how this part of the process was concealed from study personnel?

Patients in the RCTs were randomised to study treatment with interactive response technology (IRT) using computerised central randomisation. On receiving the required patient identification number and information on stratification factors, the IRT assigned the patient to the next available randomisation code within the randomisation stratum according to the specified sequence. The randomisation code was generated by the North America Clinical Supply Chain (CSC) at Teva following specifications from the Biometrics department.

A statistician who was not assigned to the study was responsible for review and approval of the randomisation code, and the final randomisation code was maintained by the CSC department. At the time of analyses, when treatment codes were revealed, the CSC department provided the randomisation codes to the statistician assigned to the study. No randomisation codes were released prior to pharmacokinetic sample analysis and thus all samples were assayed.

In the case of an emergency, the investigator could determine a patient's treatment using IRT after consultation with Teva. In an extreme emergency, and if the investigator was unable to contact Teva, the investigator could determine the patient's treatment using IRT without prior authorisation. If this occurred, the investigator had to contact the sponsor's medical monitor immediately, the patient was withdrawn from the study, and the event was recorded on the electronic case report form.

To maintain blinding of study drug, the volume of study drug (including active or placebo treatment) to be taken from each vial was assigned by IRT on the basis of the patient's body

weight and blinded treatment group. Patients and investigators remained blinded to treatment assignment during the study. Teva clinical personnel involved in the study were blinded to study drug identity until the database was locked for analysis and the treatment assignments revealed.

A12. In section 4.9.2 on page 139 and the indirect treatment comparison (Amaris report) the outcomes in the direct and indirect meta-analyses are reported imprecisely as time points ±4 weeks. Please clarify the reason for this. Three of the included RCTs reported outcomes at 4-weekly intervals, meaning that there is potential for confusion as to whether the 16±4 week time point includes data from 12, 16 and/or 20 weeks; and as to whether the 52 week time point includes data from 48 and/or 52 weeks.

The timepoints at which studies identified through the SLR reported endpoints were found to vary; for example, the EXTRA trial reported clinical outcomes at 48 weeks while most studies reported the results at 52 weeks.

To ensure that all relevant studies were considered, endpoints reported at the timepoint of interest ±4 weeks were selected. The 4-week interval was chosen based on expert opinion.

A13. With regard to section 4.14 on page 176, please provide a list of relevant ongoing studies for reslizumab in patients with asthma and elevated blood eosinophils, regardless of the evidence being available in the next 12 months.

A summary of ongoing reslizumab studies (intravenous infusion and subcutaneous formulation) is provided in Table 6.

Table 6: Ongoing reslizumab clinical development studies (subcutaneous formulation)

Study title and objectives	Sample Size	Primary Endpoint	Study Completion
Intravenous infusion			
C38072-AS-30024 (Open-label safety study of IV reslizumab in patients who were previously enrolled in study C38072/3085) Objectives: • To collect additional long-term safety data for IV reslizumab in patients with severe eosinophilic asthma	[redacted]	Safety	Ongoing
Subcutaneous formulation			
C38072-AS-30025 (Pivotal Phase III efficacy and safety study) 52-Week Double-Blind, Placebo-Controlled, Parallel-Group Efficacy and Safety Study of Reslizumab Fixed, 110 mg Subcutaneous Dosing in Patients with Uncontrolled Moderate to Severe Persistent Asthma and Elevated Blood Eosinophils. Objective: • To determine the effect of reslizumab (110 mg) administered subcutaneously every 4 weeks on CAEs in adults and adolescents with asthma and elevated blood eosinophils who are inadequately controlled on standard-of-care asthma therapy	Approximately 200 patients per treatment arm for a total of 400 patients	Frequency of CAEs per patient during the 52-week treatment period	Ongoing
C38072-AS-30027 (Oral corticosteroid-reduction study) A Phase 3, 24-Week Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy and Safety Study of Reslizumab Subcutaneous Dosing (110 mg every 4 weeks) in Patients with Oral Corticosteroid Dependent Asthma and Elevated Blood Eosinophils.	Approximately 76 patients per treatment arm for a total of 152 patients	Category of percentage reduction in daily OCS dose during Weeks 20 to 24 compared with the dose at the end of the optimisation phase.	Ongoing

Study title and objectives	Sample Size	Primary Endpoint	Study Completion
Objective: To determine the ability of reslizumab (110 mg) administered subcutaneously every 4 weeks to produce a steroid sparing effect in patients with OCS-dependent asthma and elevated blood eosinophils, without loss of asthma control.			
C38072-AS-10069 (Paediatric single-dose PK/PD study) Objective: • To characterise single-dose pharmacokinetics, safety and immunogenicity following subcutaneous administration of reslizumab in asthma patients aged 6 to <12 years of age	9 subjects per dose level, at 3 dose levels of subcutaneous reslizumab (33 mg, 110 mg and 165 mg)	PK/blood eosinophil PD	Ongoing
C38072-PK-10071 (PK site administration study and dose proportionality study) Objectives: • To evaluate dose proportionality of reslizumab over the dose range of 55–220 mg following administration of a single subcutaneous dose. • To evaluate effect of injection site on the PK of reslizumab following administration of a single subcutaneous dose.	75 subjects randomised	PK	Ongoing

Abbreviations: CAE, clinical asthma exacerbation; IV, intravenous; OCS, oral corticosteroid; PD, pharmacodynamic; PK, pharmacokinetic.

A14. The questions below relate to the *Amaris ITC report*.

- **Please could you clarify if the second analyst for the screening of titles and abstracts conducted a full 'quality' check of all the primary screening or a percentage check?**

The second analyst for the screening of titles and abstracts conducted a full 'quality' check of all primary screening. Inconsistencies/disagreements were resolved through consultation with a neutral third party.

- **What was the screening procedure for full text publications? (for example, how many reviewers were involved)**

As for the screening of titles and abstracts, the screening procedure for full text publications involved two independent reviewers. The second analyst conducted a full quality check of all primary screening. Inconsistencies/disagreements were resolved through consultation with a neutral third party.

- **Please provide the WinBUGS code used for the indirect treatment comparison.**

WinBUGS was only used for the analysis of clinically significant exacerbations. The code used in the statistical analysis of this endpoint, for both the fixed effects and random effects models, is provided in Figure 1 and Figure 2 below.

Figure 1: WinBUGS code for fixed effects model

```
# Fixed effects model for multi-arm trials
model{                                              # *** PROGRAM STARTS

for(i in 1:ns){                                     # LOOP THROUGH STUDIES
  mu[i] ~ dnorm(0,.01)                            # vague priors for all trial
                                                  #  baselines
  for (k in 1:na[i]) {                              # LOOP THROUGH ARMS
    r[i,k] ~ dpois(theta[i,k])                      # Poisson likelihood
    theta[i,k] <- lambda[i,k]*E[i,k]                # event rate * exposure
    log(lambda[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]   # model for linear
                                                        # predictor
    dev[i,k] <- 2*((theta[i,k]-r[i,k]) + r[i,k]*log(r[i,k]/theta[i,k]))#Deviance
                                                                      #contribution
  }
  resdev[i] <- sum(dev[i,1:na[i]])                  # summed residual deviance
                                                    # contribution for this trial
}
totresdev <- sum(resdev[])                          # Total Residual Deviance
d[1]<-0                                             # treatment effect is zero for
                                                    # reference treatment
for (k in 2:nt){ d[k] ~ dnorm(0,.01) }            # vague priors for treatment
                                                  # effects

# pairwise HRs and LHRs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt)) {
  for (k in 1:nt) {
    lhr[c,k] <- (d[c]-d[k])
    log(hr[c,k]) <- lhr[c,k]
    Prob.HR[c,k]<-step(d[k]-d[c])
  }
}

# ranking on relative scale
for (k in 1:nt) {
#  rk[k] <- nt+1-rank(d[],k)                        # assumes events are "good"
   rk[k] <- rank(d[],k)                             # assumes events are "bad"
   best[k] <- equals(rk[k],1)
   for (j in 1:nt){hist[j,k]<-equals(rk[k],j)}

}

for (i in 1:ns){
  AbsTrEf[i]<- mu[i]*equals(t[i,1],1)
  Nref[i]<- 1*equals(t[i,1],1)
}


}                                                 # *** PROGRAM ENDS
```

Figure 2: WinBUGS code for random effects model

```
# Poisson likelihood, log link
# Random effects model for multi-arm trials

model{                                  # *** PROGRAM STARTS
for(i in 1:ns){                         # LOOP THROUGH STUDIES
  w[i,1] <- 0                           # adjustment for multi-arm trials is zero for
                                        # control arm
  delta[i,1] <- 0                       # treatment effect is zero for control arm
  mu[i] ~ dnorm(0,.01)                # vague priors for all trial baselines
  for (k in 1:na[i]) {                      # LOOP THROUGH ARMS
    r[i,k] ~ dpois(theta[i,k])              # Poisson likelihood
    theta[i,k] <- lambda[i,k]*E[i,k]    # failure rate * exposure
    log(lambda[i,k]) <- mu[i] + delta[i,k]    # model for linear predictor
    dev[i,k] <- 2*((theta[i,k]-r[i,k]) + r[i,k]*log(r[i,k]/theta[i,k]))
                                            #Deviance contribution
  }
  resdev[i] <- sum(dev[i,1:na[i]])    # summed residual deviance contribution
                                        # for this trial
  for (k in 2:na[i]) {                  # LOOP THROUGH ARMS
    delta[i,k] ~ dnorm(md[i,k],taud[i,k])     # trial-specific LOR distributions
    md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LOR distributions (with
                                         # multi-arm trial correction)
    taud[i,k] <- tau *2*(k-1)/k          # precision of LOR distributions
                                        #(with multi-arm trial correction)
    w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]]) # adjustment for multi-arm
                                                   # RCTs
    sw[i,k] <- sum(w[i,1:k-1])/(k-1)               # cumulative adjustment for
                                                   # multi-arm trials

  }
}
totresdev <- sum(resdev[])                         #Total Residual Deviance
d[1]<-0                     # treatment effect is zero for reference treatment
for (k in 2:nt){ d[k] ~ dnorm(0,.01) }   # vague priors for treatment effects
sd ~ dunif(0,5)                            # vague prior for between-trial SD
tau <- pow(sd,-2)       # between-trial precision = (1/between-trial variance)


# pairwise HRs and LHRs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt)) {
  for (k in 1:nt) {
    lhr[c,k] <- (d[c]-d[k])
    log(hr[c,k]) <- lhr[c,k]
    Prob.HR[c,k]<-step(d[k]-d[c])
  }
}

# ranking on relative scale
for (k in 1:nt) {
#  rk[k] <- nt+1-rank(d[],k)                    # assumes events are "good"
   rk[k] <- rank(d[],k)                         # assumes events are "bad"
   best[k] <- equals(rk[k],1)
   for (j in 1:nt){hist[j,k]<-equals(rk[k],j)}

}
```

- **In table 7 of the ITC on page 35, only 17 studies are mentioned instead of 21. Does this mean 4 studies did not provide a definition of exacerbations? Unlike in the other tables of the Amaris report, there are no ticks in this table, only crosses. Do the crosses indicate that the definition is provided in a study or that all definitions are provided unless crossed?**

Yes, only 17 out of the 21 studies contained definitions of exacerbations. The following four studies did not provide a definition of exacerbations: Study 3081, Study 3084, Hoshino et al 2012, and the QUALITX trial.

In Table 7 of the indirect treatment comparison (ITC) report, crosses are used to reflect differences in definitions of exacerbations found across studies. Each column of the table corresponds to a possible component of the definition. Crosses were used to indicate when the study's definition of exacerbations included the component listed in that column.

- **Please explain why the study by Castro et al. 2011 (RES-5-0010) is omitted from table 8 on page 38 of the Amaris Report when it appears in Table 9?**

The study by Castro et al 2011 was inadvertently omitted from Table 8 of the ITC report but should indeed appear in this table. Please find the updated version of Table 8 below.

Trial number (acronym)	Population	Intervention	Comparator	Primary study reference
Study 3081	Eosinophilic	Reslizumab	Placebo/BSC	Bjermer 2015
Study 3082	Eosinophilic	Reslizumab	Placebo/BSC	Castro 2015
Study 3083	Eosinophilic	Reslizumab	Placebo/BSC	Korn 2015
Study 3084	Eosinophilic	Reslizumab	Placebo/BSC	Corren 2015
Study RES-5-0010	Eosinophilic	Reslizumab	Placebo/BSC	Castro 2011

- **Please explain the discrepancy in the number of studies listed per feasible endpoint between table 34 on page 55 and table 84 in Appendix 4.**

Discrepancies in number of studies listed per feasible endpoint between Tables 34 and 84 of the ITC report result from the fact that Table 84 presents preliminary results from the feasibility assessment. As reported in 'study selection' sections of the report (i.e. Section 3.4.1, Section 3.5.1, Section 3.6.1 etc.), some studies had missing data which prevented their inclusion in the analysis. Exact reasons for exclusion from the analysis are given in these sections of the report while Table 34 provides only a top line summary of study inclusion.

- **The text under table 37 on page 59 states that a positive change from baseline indicates that reslizumab is more effective than omalizumab for FEV1 at 16 weeks, but table 39 on page 60 states the opposite. Please provide an explanation for this discrepancy.**

This is a typo. The text under both tables should state that a positive change from baseline indicates that reslizumab is more effective than omalizumab.

2. Section B: Clarification on cost-effectiveness data

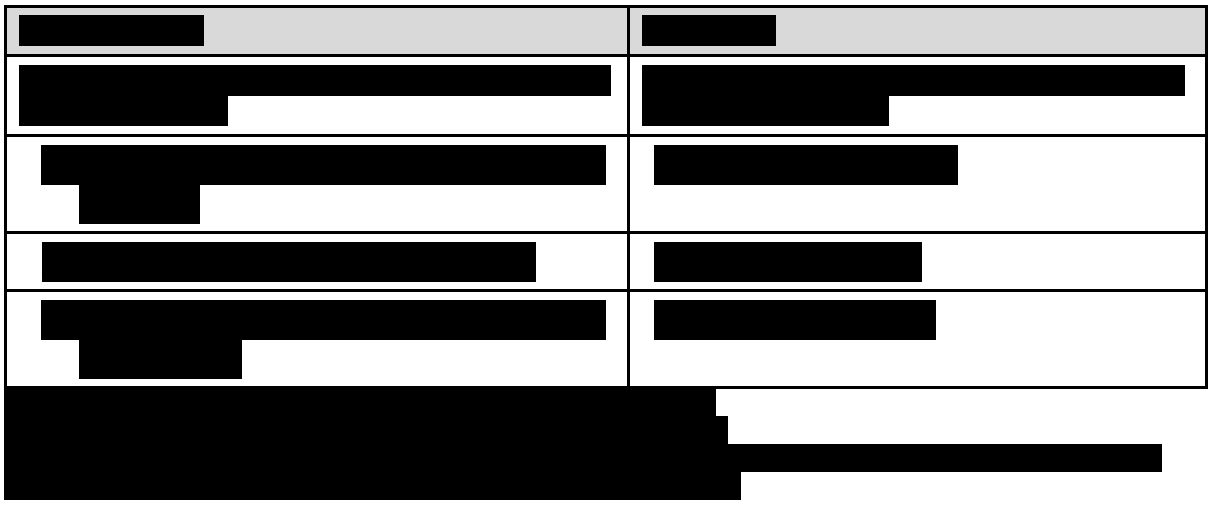
B1. Priority question: In sections 5.2.2 and 5.3.2.2 of the submission, it is indicated that "the algorithm" is used to calculate transition probabilities for weeks 0-16, weeks 16-52 and post-52 weeks. However, only the results of the algorithm were presented.

- **Please provide the full calculations necessary for determining transition probabilities and the assumptions for these calculations in an Excel spreadsheet.**

- **In a similar way please provide these details for calculating the proportion of non-responders.**

Table 7 provides a description of the responder algorithm used to calculate transition probabilities.

Table 7: Responder algorithm



Data from the pivotal clinical studies 3082 and 3083 were used to generate the responder algorithm. The pre-agreed composite definition of a clinical responder which was used in the algorithm was then also used in the cost-effectiveness model to create transition probabilities. As described on page 186 of the company submission, a patient's health state was identified at each study visit. This facilitated the tracking of health states between trial visits (every 4 weeks), allowing the calculation of the transition probabilities between the three mutually exclusive health states, 'Controlled asthma', 'Uncontrolled asthma' and 'Exacerbation' (based on frequency tables estimating the proportion of patients moving to each health state as a function of the health state at the preceding visit).

Patients were classified into the three health states at each visit using the following criteria:

- Controlled asthma: ACQ score <1.5
- Uncontrolled asthma: ACQ score ≥1.5
- Exacerbation (regardless of asthma control): If the patient suffered a moderate or a severe exacerbation since the last visit

Due to insufficient data, moderate and severe exacerbations were pooled for the computation of transition probabilities.

To delineate between moderate and severe exacerbations, the percentage of severe exacerbations (i.e. associated with the use of systemic corticosteroids) out of the total number of exacerbations reported in studies 3082 and 3083 were used: 76.3% and 81.8% of exacerbations experienced by patients in the reslizumab and placebo arms, respectively, were severe.

The model distinguishes between three periods of time for reslizumab:

- Week 0 to 16: Data from all patients between Weeks 0 and 16, regardless of their level of response at 16 weeks were considered to generate the transition matrices
- Week 16 to 52: As early non-responders are assumed to discontinue treatment at 16 weeks, the transition probabilities were estimated on the basis of responders and patients with an undetermined response (i.e. excluding non-responders), based on transitions between Weeks 16 and 52
- From Week 52: Transition probabilities were estimated based on patients identified as responders as other patients were assumed to discontinue treatment with reslizumab. As no data beyond 52 weeks of treatment were available, transitions observed between Weeks 16 and 52 were used.

Full details of transition probability calculations can be found in the separate Excel file sent to NICE with this response letter '*Appendix_2_Transition_Matrices_CIC.xlsx'*

B2. In table 117 of the company submission, it is unclear how the cost of a severe exacerbation-related hospitalisation was calculated. It is indicated that weighted average costs from the healthcare resource group (HRG codes DZ15M, DZ15N, and DZ15P are used. However, the schedules (non-elective short stay [NES], non-elective long stay [NEL], day cases [DC]) that are averaged are not provided, therefore the ERG are unable to calculate these costs. Please provide the full cost calculations for HRG codes DZ15M/N/P with clear referencing to which schedules were used.

The unit costs used to compile the severe exacerbation cost were taken from the 'Total_HRGs' worksheet of the NHS reference schedule 2014–2015 (21).

Please see the accompanying Excel file (file name: *Appendix_3_Health state-specific cost calculations_CIC.xlsx*) for details of how the health state-specific costs were calculated. A brief explanation of this spreadsheet is provided below in order to aid navigation of the document:

Column B of the spreadsheet contains the list of resources that are used in the treatment of asthma. This list was taken from a study by Willson et al (22) (see Figure 3). Column C displays the unit costs of each of these resources, as reported in the Willson study. As the Willson study was conducted some time ago, these unit costs were updated using recent and relevant values, taken from either NHS reference costs (21) or the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care 2015 (23). Exact references for these retrieved unit costs can be found in Table 120 of the company submission. Columns E to L report the resource use according to the health states used in the Willson model. The values have been altered to suit our purposes in the following ways:

- Drivers of costs were identified with clinical experts as consisting of inpatient and outpatient visits. On this basis and given the uncertainty associated with the estimates from Willson et al, the costs of lab tests/procedures and co-medication were not considered in our analysis
- Inpatient resource use was set to zero in states that don't include a severe exacerbation. This was a structural assumption in the model as, by definition, patients experiencing a severe exacerbation transition to the health state 'Severe exacerbation'.

For an explanation of the resource use adjustments, please see Section 5.5.4 of the company submission.

Figure 3: Unit costs and resource use values by health state per cycle, as in Willson et al, 2014

Table 4 Unit cost and resource use values by health state, per cycle

	Unit cost (£)[a]	Resource use per health state					
		Controlled asthma	Partly controlled asthma	Uncontrolled asthma	Non-severe exacerbation	Severe exacerbations without hospitalisation	Severe exacerbations with hospitalisation
Inpatient resource use[b]	*Cost per episode*	*Average number of events per patient per week*					
Asthma-related hospitalisation[c]	785.98	0.0034	0.0038	0.0061	0	0	0
Severe exacerbation-related hospitalisation	1,524.28	0	0	0	0	0	0.39
A&E visit only	108.22	0	0	0	0	0.058	0.00
A&E visit + hospitalisation	1,691.49	0	0	0	0	0	0.41
Ambulance + hospitalisation	1,763.93	0	0	0	0	0	0.022
Ambulance + A&E + hospitalisation	1,921.15	0	0	0	0	0	0.043
Hospitalisation including ICU stay	2,242,45	0	0	0	0	0	0.13
Outpatient visits	*Cost per visit*	*Average number of visits per patient per week*					
Visits to GP	43.00	0.031	0.039	0.14	0.60	1.37	0.59
Visits to nurse	13.69	0.050	0.068	0.16	0.43	0.90	1.38
Visits to respiratory specialist	133.26	0.016	0.033	0.094	0.094	0.34	1.76
Home visits	*Cost per visit*	*Average number of visits per patient per week*					
Visits from GP	110.00	0.00082	0.0095	0.025	0.034	0.22	0.102
Visits from nurse	37.33	0	0	0.00072	0	0.0033	0.0047
Laboratory tests/procedures	*Cost per test/procedure*	*Average number of procedures/tests per patient per week*					
Spirometry test	28.20	0.026	0.028	0.049	0.29	0.29	0.46
Flu vaccine	6.32	0.020	0.020	0.020	0	0	0
Desensitisation	175.32	0.0046	0.0077	0.0087	0	0	0
Co-medication	*Cost per mg*	*Average number of patients using each co-medication per week*					
Prednisone	0.067	0.29	0.34	0.51	0.57	0.81	0.87
Amoxicillin	0.00015	0	0	0.30	0.54	0.71	0.70
Singulair	0.17	0	0	0.83	0	0	0
Hydrocortisone IV	0.011	0	0	0	0	0	0.81
Magnesium IV	0.0033	0	0	0	0	0	0.74

A&E accident and emergency department, *GP* general practitioner, *ICU* intensive care unit, *IV* intravenous,

[a] All costs are given in 2012 pounds sterling (£). Sources of unit costs have been specified in Sect. 2.4.3

[b] All inpatient resource use has been derived from the PrimoTinA-asthma® clinical trials

[c] An asthma-related hospitalisation that is not a result of an exacerbation

To calculate health state-specific costs for the 'Uncontrolled asthma' health state, the levels of resource use were multiplied by the unit costs. For the 'Controlled asthma' health state, a weighted average of the 'Controlled' and 'Partly controlled' health state costs were taken due to difference in definitions of health states between the present study and the study by Willson et al. The weights were based on the proportion of time spent in 'Partly controlled asthma' (ACQ of 1–1.5) and 'Controlled asthma' (ACQ <1) in the 3082 and 3083 trials. The 'Moderate exacerbation' cycle cost was assumed to consist of one week treating a non-severe exacerbation and three weeks of being in the 'Uncontrolled asthma' health state. The mean cost of severe exacerbation was a weighted average of the cost of severe exacerbations leading and not leading to hospitalisation.

B3. The ERG was unable to identify HRG code DA15QR which is referenced in table 117, page 206 of the company's submission. Please indicate the source of this code or supply a corrected code.

The code in question (DA15QR) does not correspond to an HRG code and should not appear in Table 117 of the company submission. The code that should be reported is DZ15M/N/P (21).

DZ15M/N/P signifies a weighted average of three codes (defined below) that was used to calculate the cost of a 'Severe exacerbation-related hospitalisation'.

- DZ15M – 'Asthma with Interventions'
- DZ15N – 'Asthma without Interventions, with CC Score 9+'
- DZ15P – 'Asthma without Interventions, with CC Score 6–8'

B4. In table 121, page 212 of the submission, costs derived from table 120 on the previous page are synthesised into aggregate values for each health state. The ERG tried synthesising the costs to reproduce table 121, but were unable to do so. Please explain the discrepancy between the two tables and please provide an Excel spreadsheet with calculations for health state costs in the model.

Please see the Excel file sent to NICE with this response letter (file name: *Appendix_3_Health state-specific cost calculations_CIC.xlsx*). This spreadsheet details all of the unit costs and background calculations that have contributed to the final health state costs used in the model.

Table 120 in the company submission presents the unit costs and resource use by health state. Unit costs were applied to the levels of healthcare resource use by health state and the corresponding estimates are reported in Table 121 of the submission. Details of the calculations are included in the Excel file.

B5. Table 138 on page 236 of the company submission provides the results of a scenario analysis using utility data mapped from the Asthma Quality of Life Questionnaire (AQLQ) using an algorithm by Tsuchiya and colleagues. Please provide complete details of the data used for mapping, including: how patients were matched

to the health states, the AQLQ values that correspond to these health states, and the mapped EQ-5D values that correspond to these health states.

Mapping was performed based on the algorithm described by Tsuchiya et al (24). Using Model 4 (results from the other models are not in the public domain and thus only Model 4 was used) and the covariates in Appendix 3a in this article, the following algorithm was defined: A single EQ-5D should be calculated using 10 questions from AQLQ, for every patient, for every visit for studies 3082 and 3083 using the following equation:

$$\mathbf{EQ5D} = 0.2329 - 0.0282\,X_{1,2} + 0.0079\,X_{1,3} + 0.0532\,X_{1,4} + 0.0408\,X_{1,5} + 0.0479\,X_{1,6} + 0.0604\,X_{1,7}$$
$$- 0.0381\,X_{3,2} - 0.0221\,X_{3,3} + 0.0222\,X_{3,4} + 0.2613\,X_{3,5} + 0.0385\,X_{3,6} + 0.0469\,X_{3,7}$$
$$+ 0.0935\,X_{5,2} + 0.0618\,X_{5,3} + 0.0757\,X_{5,4} + 0.1047\,X_{5,5} + 0.1232\,X_{5,6} + 0.1304\,X_{5,7}$$
$$- 0.1723\,X_{6,2} + 0.1101\,X_{6,3} + 0.0873\,X_{6,4} + 0.1138\,X_{6,5} + 0.1061\,X_{6,6} + 0.1055\,X_{6,7}$$
$$+ 0.0119\,X_{25,2} + 0.0308\,X_{25,3} + 0.0602\,X_{25,4} + 0.0724\,X_{25,5} + 0.0577\,X_{25,6} + 0.0816\,X_{25,7}$$
$$- 0.0163\,X_{26,2} + 0.0085\,X_{26,3} - 0.0037\,X_{26,4} + 0.0091\,X_{26,5} + 0.0302\,X_{26,6} + 0.0215\,X_{26,7}$$
$$+ 0.0512\,X_{27,2} + 0.0572\,X_{27,3} + 0.0693\,X_{27,4} + 0.0727\,X_{27,5} + 0.0749\,X_{27,6} + 0.0727\,X_{27,7}$$
$$- 0.0110\,X_{29,2} - 0.0080\,X_{29,3} + 0.0163\,X_{29,4} + 0.0045\,X_{29,5} + 0.0273\,X_{29,6} + 0.0338\,X_{29,7}$$
$$+ 0.0934\,X_{31,2} + 0.0263\,X_{31,3} + 0.0648\,X_{31,4} + 0.0946\,X_{31,5} + 0.1192\,X_{31,6} + 0.1197\,X_{31,7}$$
$$- 0.0853\,X_{32,2} - 0.0036\,X_{32,3} + 0.0195\,X_{32,4} + 0.0069\,X_{32,5} + 0.0316\,X_{32,6} + 0.0254\,X_{32,7}$$

Where:

$X_{i,j}$ = indicator for the result for AQLQ question i, namely: $X_{i,j} = 1$ if Result for question i is j, 0 otherwise.

Examples:

If QSTESTCD = 'AQLQ029' and QSSTRESC = 3 then:

$X_{29,2}=0$, $X_{29,3}=1$, $X_{29,4}=0$, $X_{29,5}=0$, $X_{29,6}=0$, $X_{29,7}=0$

If QSTESTCD = 'AQLQ029' and QSSTRESC = 1 then:

$X_{29,2}=0$, $X_{29,3}=0$, $X_{29,4}=0$, $X_{29,5}=0$, $X_{29,6}=0$, $X_{29,7}=0$

B6. Please describe what changes need to be made to the economic model to produce the subgroup analyses for adult patients classified as GINA step 4/5 in table 144 on page 238 of the company's submission.

The results presented in Table 144 of the company submission were obtained by running the analysis based on all GINA step 4/5 adult patients enrolled in the 3082 and 3083 trials to estimate transition probabilities. [redacted]

[redacted]

B7. In the estimation of the transition probabilities, the company used the actual transition between health states from the two pivotal trials. However, the number of patients in each health state as stated in table 102 on page 186 does not match the number of patients in the model worksheet named "Sheet1" in the economic model. Please explain the differences in these numbers?

The 'Actual transition', and 'Total' columns in Sheet 1 of the model worksheet do not refer to patient numbers. These numbers refer to the number of transitions between study visits (as trial visits occurred every 4 weeks).

For example, the value of 784 reported in cell H8 of Sheet 1 means that there has been a total of 784 transitions from the uncontrolled health state by adult GINA 4/5 patients being treated with reslizumab in the period from baseline to 16 weeks (i.e. between baseline and visit 1, visit 1 and visit 2, visit 2 and visit 3, and visit 3 and visit 4).

B8. On page 239, the company states that a multiplier of 1.535 was applied to match the annual rate of exacerbation of 2.06 in the BSC arm, using the transition probabilities based on all adult patients at GINA Steps 4 and 5. Please clarify how the multiplier used to estimate the risk of exacerbations has been calculated.

To reflect the rates of exacerbations expected to be observed in clinical practice, a multiplier was applied to the probabilities of transitioning to the exacerbation health states to match the mean annual rates of exacerbations observed in the year preceding enrolment in the clinical trials. The same multiplier was applied to all probabilities of moving to the exacerbation health states (i.e. for each treatment arm, the probability of moving to an exacerbation health state was multiplied by the same coefficient, thereby maintaining the relative treatment effect).

For each subgroup, the multiplier was estimated so that the annual rate of exacerbations in the BSC arm matched the mean rate of exacerbations in the year preceding enrolment in the 3082 and 3083 trials for the subgroup of interest (see Table 102 on page 186 of the company submission).

As the mean rate of exacerbation increases as a function of the multiplier, an iterative process was used to estimate each multiplier.

3. Section C: Textual clarifications and additional points

C1. As the Teva treatment algorithm is yet to be published, it is therefore marked as academic in confidence. However, for a treatment algorithm to effectively address the unmet need, it should be made publicly available to the specialists who would use it. Is there a known publication date for the treatment algorithm? Has the treatment algorithm been endorsed by any asthma specialists?

An abstract and poster reporting the treatment algorithm will be available at the European Respiratory Society meeting in London on September 3–7th 2016. A manuscript is in preparation for publication but there is no final date for publication yet. The treatment algorithm has been reviewed and endorsed by several expert asthma specialists in the UK.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Reslizumab for treating eosinophilic asthma inadequately controlled on inhaled corticosteroids [ID872]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Asthma UK

Your position in the organisation: Senior Policy Officer

Brief description of the organisation: Asthma UK is the UK's leading asthma charity. We support people with asthma when they need us the most and fund world-leading research to find better treatments and ultimately a cure. Our goal is to prevent asthma attacks, especially those that result in death and emergency hospitalisation.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: Asthma UK receives no funding from the tobacco industry.

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Asthma is one of the most prevalent long-term conditions in the UK, with 5.4 million people currently receiving treatment. Severe asthma affects nearly 5% of people with asthma – around 250,000 people, of whom a subgroup of around 20% will have an eosinophilic phenotype.[1] The National Review of Asthma Deaths highlighted that almost 40% of those who died had severe asthma.[2]

Severe asthma is a cluster of types of asthma that do not respond to current readily available treatments, rather than simply an extreme form of the condition. It requires more intensive and expensive therapies to control symptoms to prevent attacks, hospitalisations and deaths. People with the most severe asthma represent a particular challenge: they not only suffer greater morbidity, but they also fall outside the robust evidence base that

[1] Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, Wardlaw AJ, Green RH. Cluster analysis and clinical asthma phenotypes. Am J Respir Crit Care Med 2008; 178: 218-224.

[2] Royal College of Physicians. Why asthma still kills: The National Review of Asthma Deaths; 2014.

informs most asthma care, requiring specialist attention, treatment and pathways.[3]

Ongoing severe symptoms and a complex medicine regime are often accompanied by frequent hospital admissions for many people with severe asthma. Numerous hospital admissions to respiratory wards, intensive care units (ITU) and high dependency units lead to further social isolation and economic disadvantage for people affected by asthma as well as high costs to the NHS. Studies looking at the information gathered through the Difficult Asthma Registry have estimated that clinical costs for severe asthma are between £2912 to £4217 per person, per year made up of GP/A&E appointments, asthma medication, scheduled GP/A&E attendance, hospital admission, outpatient review, non-medication costs and ITU.[4] The costs for people on maintenance oral corticosteroids were 43% higher and where people had two or more exacerbations and oral corticosteroid courses the costs were 31% higher than those with less than two courses of treatment with oral corticosteroids. Overall, the costs are significantly higher than for people with controlled asthma which a recent study estimated at £451 per person, per year.[5]

People with severe asthma have highlighted to us the extent that living with the condition affects their lives, as described below.

"[Severe asthma] affects me every day, simple everyday things are triggers, going out places can be difficult due to strong fragrances, air fresheners, dust, mould spores, pollen and so very much more. A simple cold can go straight to your chest and end you up in hospital fighting for your life. The steroids we have to take affects your body badly and can cause multiple illnesses, yet it's one of the only things that helps with the swellings in the airways. Sleeping is a nightmare, when you manage to get any sleep you often wake up gasping for breath as you're going into a full attack."

[3] Wenzel S. Characteristics, definition and phenotypes of severe asthma. In: Chung KF, Bel E, Wenzel S, editors. ERS Monograph: Difficult-to-Treat Severe Asthma. 51: European Respiratory Society; 2011.
[4] O'Neill et al, 2016, Thorax http://dx.doi.org/10.1136/thoraxjnl-2013-204114
[5] Ibid

"Every day has to be planned regimentally in advance when you are dependent on nebulisers (battery ones just aren't as strong). At the same time though, you can't make plans in advance because your chest can kick off at any time and plans often have to be cancelled last minute."

"I am still very nearly housebound because I can't breathe well enough to walk more than a few steps much of the time. I get out an average of twice a week at the moment, have had to give up work, move home etc, because my body simply won't allow me to live what would usually be considered a normal life."

"Life is chaotic with severe asthma. It can be impossible to work as you cannot commit to a regular schedule - I cannot go out if it is raining, humid, low temperatures, foggy, pollution levels or pollen are high, because of the risk of attack…yesterday I did a food shop, today I can't walk from the lounge to the kitchen to make a drink but I have taken the same medications today that kept the condition under control yesterday. We bear a huge psychological burden living in fear of the next attack and watching our families struggle to cope with our illness. There is no cure, little control, financial hardship - including having to pay for medicines and constant rounds of hospital/doctors appointments."

The impact on everyday relationships was also highlighted in Asthma UK's 2011 report *Fighting for Breath*:

"With the constant need to make compromises for severe asthma, relationships can suffer…The impact of caring for someone with severe asthma is substantial – many parents struggle to maintain a job because their child needs their support. This doesn't just affect parents – other family members, or even children can also be carers. Sadly, because asthma isn't usually seen as something that has a big impact, those who spend a lot of time caring for people with severe asthma get even less recognition and support than other carers."

One prospective cohort study of 465 adults in the US with severe asthma found that 14% of people with severe asthma are unable to work, and among

those in employment, partial disability preventing full-time work was 38%.[6] In a Europe-wide survey of people with severe asthma,16% in the UK found that their asthma restricted their employment prospects.[7]

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Keeping symptoms under control is the main goal of asthma treatment, but the reality for some people with severe asthma is that this is not possible with current standard treatments.[8] It is therefore important for new treatment options to help people better control their symptoms to prevent potentially life-threatening asthma attacks, and enable them to stay socially active and remain in employment.

People with severe asthma have to find a way to cope with dangerous and frustrating symptoms. Persistent symptoms can lead to lack of sleep, social isolation, feelings of despair and depression, low activity levels, weight gain and increased dependence on family and carers. [9]

As highlighted from comments we have received from people with severe asthma, many people are concerned at the ineffectiveness of current treatments to maintain control, in addition to the side-effects associated with treatment. New treatments for people with severe asthma should therefore have oral corticosteroid reduction as a key aim.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

Specialised centres, commissioned by NHS England, are fundamental to the successful delivery of severe asthma care, using innovative care models to ensure appropriate diagnosis, and use of existing and new high-cost

[6] Eisner MD, Yelin EH, Katz PP, Lactao G, Iribarren C, Blanc PD. Risk factors for work disability in severe adult asthma. Am J Med. 2006 Oct;119(10):884-91.
[7] Dockrell M, Partridge MR, Valovirta E. The limitations of severe asthma: the results of a European survey. Allergy. 2007 Feb;62(2):134-41
[8] Hotgate ST and Polosa R, The mechanisms diagnosis and management of severe asthma in adults *Lancet* 2006, 368: 780-93
[9] Asthma UK. Fighting for Breath; 2011

medications. Specialist centres only cater for a small proportion of the severe asthma population, serving as a gateway for access to more specialised treatments.

People with severe asthma can often find themselves taking very high doses of medicines for a long time. The side effects of these medicines, especially long-term oral corticosteroids, are often very serious. These include osteoporosis, psychological symptoms, Cushing's syndrome, adrenal failure, diabetes, growth retardation, high blood pressure, cataracts and Addison's disease.[10,11,12,13]

Research evidence assessing rates of side effects from oral corticosteroids specifically among people with severe asthma is limited, though a meta-analysis of their use in people with inflammatory diseases found an average adverse event rate of 150 per 100 patient-years, with much higher rates in some groups.[14] A recent study by Sweeney et al., published online earlier this year, presents data from two large severe asthma populations (the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry) and shows that OCS use results in a higher prevalence of comorbidities - including type II diabetes, hypertension and osteoporosis.[15] This should be factored into any calculations made to determine reslizumab's incremental cost-effectiveness ratio (ICER), in addition to quality-of-life benefits to carers.

In reaching out to people with severe asthma for their views on living with the condition, several highlighted their experience of current care and treatments – with many concerned at the side-effects. These are presented below:

[10] Stuart FA, Segal TY, Keady S. Adverse psychological effects of corticosteroids in children and adolescents. Arch Dis Child. 2005 May;90(5):500-6.
[11] Weldon D. The effects of corticosteroids on bone growth and bone density. Ann Allergy Asthma Immunol. 2009 Jul;103(1):3-11;, 50.
[12] Blackburn et al, Quantification of the Risk of Corticosteroid-induced Diabetes Mellitus Among the Elderly, J Gen Intern Med. 2002 September; 17(9): 717–720.
[13] BTS/SIGN op cit
[14] Hoes JN et al, Adverse events of low- to medium-dose oral glucocorticoids in inflammatory diseases: a meta-analysis. Ann Rheum Dis. 2009 Dec;68(12):1833-8. Epub 2008 Dec 9.
[15] Sweeney J, Patterson CC, Menzies-Gow A, Niven RM et al. Comorbidity in severe asthma requiring systemic corticosteroid therapy: cross-sectional data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry. Thorax 2016;71:339-346 doi:10.1136/thoraxjnl-2015-207630

"It's terrifying. Not knowing when you're going to next be in hospital. You can't make plans for fear of having to cancel. Your body is distorted from all the medication and you end up on more medication to deal with the side effects of the medication that keeps you alive…It feels like a life sentence at times and not only to you but to your family too. Unless you live with severe asthma you have no idea what it is like."

"Every day seems to be an uphill struggle to control asthma symptoms…it's always hard to breath and taking inhalers and tablets for Asthma on a daily basis just to survive can be daunting...and when you have an attack it can be quite scary…having to have a nebulizer and steroid treatment can take its toll on your body…steroids change your personality and I become aggressive on them"

"I have reached a point where the side-effects of treatment (steroid side-effects, insomnia, weight gain, fungal infections, concerns and tests regarding bone density etc) are becoming almost as persistent and unpleasant as the asthma symptoms they are treating."

"Much of the day can be taken up with nebulised treatments, frequent taking of medications – for me that is 13 different prescriptions, some taken more than once a day."

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)

- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

Unfortunately, we have not received views to-date from people with severe eosinophilic asthma that have been treated with reslizumab. However, as mentioned above people with severe asthma are consistently concerned with the difficulty in maintaining control using the current treatments available, in addition to the side-effects that they experience. From our experience with omalizumab, we have seen how OCS use can be reduced in people with severe allergic asthma – as shown through a 2-year, international and observational registry, conducted in a real-life setting.[16]

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

There is a substantial unmet need for people with severe asthma in the treatment options available to them. People with severe asthma have very limited treatment options that involve high doses of drugs with very poor side effect profiles. Reslizumab could provide an alternative option for people with severe eosinophilic asthma that do not respond well to current treatments.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

N/A

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse

[16] Braunstahl G-J, Chlumský J, Peachey G, Chen C-W. Reduction in oral corticosteroid use in patients receiving omalizumab for allergic asthma in the real-world setting. Allergy, Asthma, and Clinical Immunology : Official Journal of the Canadian Society of Allergy and Clinical Immunology. 2013;9(1):47. doi:10.1186/1710-1492-9-47.

- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

As highlighted above, people with severe asthma almost always find themselves taking very high doses of medicines for a long time and the side effects of these medicines, especially long-term OCS, are often very serious. From a patient perspective, reduced oral corticosteroid use is therefore a key priority of any future treatment.

Please list any concerns patients or carers have about the treatment being appraised.

N/A

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

N/A

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Around 250,000 people are estimated to have severe asthma, of which a subgroup of around 20% will have an eosinophilic phenotype. This new treatment is specifically targeted to reduce severe asthma attacks by reducing the levels of blood eosinophils associated with the condition. It is therefore logical that this subgroup of people with severe asthma could potentially benefit more than the broader severe asthma group.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

As reslizumab is targeted at reducing the levels of blood eosinophils associated with severe asthma, those with severe asthma who do not have an eosinophilic phenotype may benefit less from the treatment.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

Yes

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

N/A

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

We note that reslizumab has performed well in Phase III trials for patients with inadequately controlled asthma and a blood eosinophil concentration of 400 cells per μL or more, with patients showing a significant reduction in the frequency of asthma exacerbations.[17] Patients also experienced significantly improved quality of life scores compared to placebo as measured by the Asthma Quality of Life Questionnaire, seven-item Asthma Control Questionnaire, and Asthma Symptom Utility Index.

It is important that these improvements in quality of life are fully taken into account when determining reslizumab's ICER. Severe asthma is a condition where between attacks patients can be considered well in between

[17] Castro M, Zangrilli J, Wechsler ME, Bateman ED et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med 2015; 3: 355–66

exacerbations of their condition. However, quality of life is severely impaired during attacks and, in many patients with severe eosinophilic asthma, by the treatment required to treat and prevent these attacks. The asthma-specific quality of life measures capture this to a greater degree than general instruments to measure health outcomes (such as EQ-5D). Indeed, a review that considered the performance of EQ-5D for asthma found that while EQ-5D demonstrated validity in the majority of known group comparisons, disease specific measures such as AQLQ did show a greater degree of responsiveness than the generic measures.[18] This is important, as while EQ-5D is effective in capturing some measures of patients' health-related quality of life, often these are not key issues for people with severe asthma.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

Yes

If yes, please provide references to the relevant studies.

Asthma UK. Fighting for Breath; 2011

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;

[18] Wailoo A, Davis S, Tosh J. The incorporation of health benefits in cost utility analysis using the EQ-5D. Report by the Decision Support Unit; 2010.

- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

As mentioned previously, there is a substantial unmet need for people with severe asthma in the treatment options available to them. People with severe asthma have very limited treatment options that involve high doses of drugs with toxic and damaging side effect profiles and significant long-term health impacts.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

9. Other issues

Do you consider the treatment to be innovative?

Yes

If yes, please explain what makes it significantly different from other treatments for the condition.

As highlighted above, there is a substantial unmet need for people with severe asthma in the treatment options available to them. This treatment could offer an alternative and potentially more effective treatment option to a specific subgroup of those with the condition.

Are there any other issues that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Severe asthma affects nearly 5% of people with asthma – around 250,000 people, of whom a subgroup of around 20% will have an eosinophilic

phenotype that might benefit from reslizumab. The National Review of Asthma Deaths highlighted that almost 40% of those who died had severe asthma.

- People with severe asthma do not respond to standard treatment and require more intensive and expensive therapies to control symptoms to prevent attacks, hospitalisations and deaths. There is a substantial unmet need for people with severe asthma in relation to treatment options.
- People with severe asthma can often find themselves taking very high doses of medicines for a long time. The side effects of these medicines, especially long-term oral corticosteroids, are often very serious and of great concern and distress to people with severe asthma. This impact needs to be factored into the incremental cost-effectiveness ratio.
- Ongoing severe symptoms and a complex medicine regime are often accompanied by frequent hospital admissions for many people with severe asthma.
- This treatment could offer an alternative and potentially more effective treatment option to those people with severe asthma that have an eosinophilic phenotype.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Reslizumab for treating eosinophilic asthma inadequately controlled on inhaled corticosteroids [ID872]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: British Society for Allergy and Clinical Immunology
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? YES
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? YES
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? YES Consultant Physician University Hospitals of Leicester NHS Trust
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: NO LINKS or FUNDING

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Reslizumab for treating eosinophilic asthma inadequately controlled on inhaled corticosteroids [ID872]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Reslizumab will be aimed at patients with eosinophilic disease whose asthma is not well controlled with high dose inhaled steroids and long acting bronchodilators (>step 3 of the British Thoracic Society guidelines). They therefore have difficult to control asthma. Assuming the diagnosis is correct and the patients are taking their treatment as prescribed (often quite significant assumptions), these patients have severe asthma which requires additional treatment. Severe asthma may be expressed as poor symptom control or frequent exacerbations or a combination of the two. Severe eosinophilic asthma usually requires systemic corticosteroids given as either short courses of high dose steroids for one to two weeks or continuous low dose corticosteroids usually 5 to 10 mg day. Patients who are atopic (i.e have raised specific IgE to a common aeroallergen) may be treated with omalizumab, a biological therapy that binds IgE. If the patient does not have atopy then treatment options include other immunosuppressants such as methotrexate or azathioprine, but they do not have a strong evidence base to support their use for asthma and they have generally modest benefit at best with the risk of serious side effects.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Asthma broadly speaking can be divided into eosinophilic (about 80%) and non-eosinophilic disease. Eosinophilic disease is closely associated with exacerbation prone asthma where people develop flares which are relatively unresponsive to bronchodilators but usually respond well to systemic corticosteroids. Exacerbations are responsible for admissions to hospital and in extreme cases death. The relevant sub-group of asthmatics for this treatment are those with uncontrolled eosinophilic asthma who are exacerbation prone

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Reslizumab for treating eosinophilic asthma inadequately controlled on inhaled corticosteroids [ID872]

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

This treatment will be prescribed in secondary care after assessment by a NHS England recognised severe asthma service which has been established throughout England and Wales. These services are multi-disciplinary and include physicians with sub-specialist expertise in the management of asthma, specialist nurses, physiotherapists, speech therapists, pharmacists and psychologists. This ensures that those patients who present with difficult to control asthma have genuine severe asthma which justifies the use of an expensive biological therapy. They can also guide and supervise the appropriate delivery and follow up of the therapy which may be given in the patient's local hospital

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Not current available

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

There are numerous guidelines for the management of asthma in general and severe asthma in particular. The main guideline that is followed in the UK is the British Thoracic Society-Scottish Intercollegiate Guidelines Network guideline on the Management of Asthma last updated in 2014. These have been published since the early 1990's and use a high quality methodology. They are widely respected and followed.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

Most asthma treatment is self-delivered so this is a departure from standard care. It will require attendance at hospital for up to two hours because of the risk of anaphylaxis in most cases once a month which is a burden on patient time as well as expensive to deliver. Unlike omalizumab and if approved

mepolizumab) I believe it is given intravenously which is somewhat more onerous as it will require venous access. Like omalizumab and mepolizumab this treatment appears generally safe and well tolerated

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Inclusion criteria should include demonstration of eosinophilic asthma as shown by a blood eosinophil count of >0.3x109/L in the previous 2 months, and asthma which is poorly controlled in terms of severe exacerbations either by a need for 4 or more course of oral steroids a year or continuous oral steroids. There should be objective evidence that patients are taking their inhaled corticosteroids as prescribed. Patients should be closely monitored and the treatment stopped after one year if there has not been a significant (~50%) reduction in oral steroid requirement or exacerbations. The patients should continue to be monitored at six monthly intervals to make sure they are still clinically benefitting from the treatment.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The clinical trials were a reasonable surrogate of practice in the UK and the type of patients who will be eligible for treatment. The studies which had exacerbations as the primary outcome are most relevant to the rationale for treating patients with reslizumab.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Reslizumab appears to be generally well tolerated with few significant adverse events. I have no concerns on this issue.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Reslizumab for treating eosinophilic asthma inadequately controlled on inhaled corticosteroids [ID872]

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

No

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The asthma community is generally prepared for the introduction of new biological therapies for asthma and I would expect that difficult asthma clinics in England and Wales would be able to start delivering it within the 3 month time period

Equality

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Reslizumab for treating eosinophilic asthma inadequately controlled on inhaled corticosteroids [ID872]

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

I don't believe there are any equality issues with this medication

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Reslizumab for treating eosinophilic asthma inadequately controlled on inhaled corticosteroids [ID872]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: British Thoracic Society.
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? X
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)
-

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

None

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The place for the technology would be expected to be used in severe asthmatics at step 4-5 of the current British Thoracic Society / SIGN guidelines for the treatment of asthma. It would be expected to be used in those patients with persistent symptoms despite this level of treatment with poor asthma control and recurrent asthma attacks (exacerbations). There are no current alternatives. Omalizumab may be considered but has a different mechanism of action in that it targets IgE and therefore an atopic phenotype whereas this technology targets IL5 or Eosinophilic phenotypes of asthma and therefore a different population. This would allow a different subset of patients with asthma who currently have no other alternative to be treated and receive benefit.
The technology would be expected to be used in the context of a tertiary specialist asthma clinic as per NHS England service specifications:L Specialist commissioning.
The technology is currently not widely available.

Relevant guideline documents:
Current BTS/SIGN asthma guideline (update to be published in summer 2016)

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Single Technology Appraisal (STA)

Reslizumab for treating eosinophilic asthma inadequately controlled on inhaled corticosteroids [ID872]

https://www.brit-thoracic.org.uk/document-library/clinical-information/asthma/btssign-asthma-guideline-2014/

NHSE Severe asthma:
https://www.england.nhs.uk/wp-content/uploads/2013/06/a14-respiratory-sev-asthma.pdf

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The advantages are that this will potentially offer further options for care of patients that have exhausted all other alternatives or standard care. The technology will involve regular visits to clinics and facilities to administer it. It may also allow the avoidance of long term oral corticosteroid use with the reduction of the adverse effects of this: i.e. reduced risk of cataracts, osteoporosis, infections, osteonecrosis, skin thinning etc.
Patients would likely need formal assessment in a dedicated specialist asthma clinic commissioned to see severe asthma patients with the appropriate work up.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Reslizumab for treating eosinophilic asthma inadequately controlled on inhaled corticosteroids [ID872]

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Nil at this point

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The delivery of the medication is likely to be through NHSE specialist commissioned centres.

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Single Technology Appraisal (STA)

Reslizumab for treating eosinophilic asthma inadequately controlled on inhaled corticosteroids [ID872]

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

As patients would likely need assessment in regional specialist commissioned severe asthma centres. Those who are unable or unwilling to travel may potentially be discriminated against as they would not have access to the medication.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Reslizumab for treating eosinophilic asthma inadequately controlled on inhaled corticosteroids [ID872]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: XXXXXXXXXXXXX

Name of your organisation British Society for Clinical Allergy and Immuology

Are you (tick all that apply):

X a specialist in the treatment of people with the condition for which NICE is considering this technology?

X a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?

- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

No Links

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Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Reslizumab will be aimed at patients with eosinophilic disease whose asthma is not well controlled with high dose inhaled steroids and long acting bronchodilators (>step 3 of the British Thoracic Society guidelines). They therefore have difficult to control asthma. Assuming the diagnosis is correct and the patients are taking their treatment as prescribed (often quite significant assumptions), these patients have severe asthma which requires additional treatment. Severe asthma may be expressed as poor symptom control or frequent exacerbations or a combination of the two. Severe eosinophilic asthma usually requires systemic corticosteroids given as either short courses of high dose steroids for one to two weeks or continuous low dose corticosteroids usually 5 to 10 mg day. Patients who are atopic (i.e have raised specific IgE to a common aeroallergen) may be treated with omalizumab, a biological therapy that binds IgE. If the patient does not have atopy then treatment options include other immunosuppressants such as methotrexate or azathioprine, but they do not have a strong evidence base to support their use for asthma and they have generally modest benefit at best with the risk of serious side effects.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Asthma broadly speaking can be divided into eosinophilic (about 80%) and non-eosinophilic disease. Eosinophilic disease is closely associated with exacerbation prone asthma where people develop flares which are relatively unresponsive to bronchodilators but usually respond well to systemic corticosteroids. Exacerbations are responsible for admissions to hospital and in extreme cases death. The relevant sub-group of asthmatics for this treatment are those with uncontrolled eosinophilic asthma who are exacerbation prone

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

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Single Technology Appraisal (STA)

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

This treatment will be prescribed in secondary care after assessment by a NHS England recognised severe asthma service which has been established throughout England and Wales. These services are multi-disciplinary and include physicians with sub-specialist expertise in the management of asthma, specialist nurses, physiotherapists, speech therapists, pharmacists and psychologists. This ensures that those patients who present with difficult to control asthma have genuine severe asthma which justifies the use of an expensive biological therapy. They can also guide and supervise the appropriate delivery and follow up of the therapy which may be given in the patient's local hospital

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

There are numerous guidelines for the management of asthma in general and severe asthma in particular. The main guideline that is followed in the UK is the British Thoracic Society-Scottish Intercollegiate Guidelines Network guideline on the Management of Asthma last updated in 2014. These have been published since the early 1990's and use a high quality methodology. They are widely respected and followed

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

Most asthma treatment is self-delivered so this is a departure from standard care. It will require attendance at hospital for up to two hours because of the risk of anaphylaxis in most cases once a month which is a burden on patient time as well as expensive to deliver. Unlike omalizumab and if approved mepolizumab) I believe it is given intravenously which is somewhat more onerous as it will require venous access. Like omalizumab and mepolizumab this treatment appears generally safe and well tolerated

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements

for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Inclusion criteria should include demonstration of eosinophilic asthma as shown by a blood eosinophil count of >0.3x109/L in the previous 2 months, and asthma which is poorly controlled in terms of severe exacerbations either by a need for 4 or more course of oral steroids a year or continuous oral steroids. There should be objective evidence that patients are taking their inhaled corticosteroids as prescribed. Patients should be closely monitored and the treatment stopped after one year if there has not been a significant (~50%) reduction in oral steroid requirement or exacerbations. The patients should continue to be monitored at six monthly intervals to make sure they are still clinically benefitting from the treatment.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The clinical trials were a reasonable surrogate of practice in the UK and the type of patients who will be eligible for treatment. The studies which had exacerbations as the primary outcome are most relevant to the rationale for treating patients with reslizumab.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Reslizumab appears to be generally well tolerated with few significant adverse events. With biological therapies there is a low risk of an allergic reaction which is why initially at least the drug should be given in hospital. The drug has only been given to a relatively small number of people and rare side effects may come to light when it starts to be used in clinical practice.

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Single Technology Appraisal (STA)

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

There are no equality and diversity issues with this drug that I am aware of assuming as an expensive drug access is uniform across England and Wales.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

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Single Technology Appraisal (STA)

No

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The asthma community is generally well prepared for the introduction of new biological therapies for asthma and I would expect that difficult asthma clinics in England and Wales would be able to start delivering it within the 3 month time period

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Single Technology Appraisal (STA)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Reslizumab for treating eosinophilic asthma inadequately controlled on inhaled corticosteroids [ID872]]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. *About you*

Your name:
Name of your nominating organisation: Asthma UK
Do you know if your nominating organisation has submitted a statement?

✓ Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

✓ Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

☐ Yes ☐✓ No

- a carer of a patient with the condition?

☐ Yes ✓☐ No

- a patient organisation employee or volunteer?

✓☐ Yes ☐ No

Do you have experience of the treatment being appraised?

☐ Yes ✓☐ No

If you wrote the organisation submission and do not have anything to add, tick here ✓☐ (If you tick this box, the rest of this form will be deleted after submission.)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

Please list any concerns you have about the treatment being appraised.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. *Equality*

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

9. *Other issues*

Do you consider the treatment to be innovative?

☐ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Is there anything else that you would like the Appraisal Committee to consider?

10. *Key messages*

In no more than 5 bullet points, please summarise the key messages of your submission.

-
-
-
-
-

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Single Technology Appraisal (STA)

Reslizumab for treating eosinophilic asthma inadequately controlled on inhaled corticosteroids [ID872]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: XXXXXXXXXXXXXXXXXX

Name of your organisation: **Royal College of Physicians**

Are you (tick all that apply):

a specialist in the treatment of people with the condition for which NICE is considering this technology? √

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

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Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

The mechanisms leading to asthma are heterogenous with considerable variations in severity and complexity best expressed as the relationship between airway dysfunction as measured by variability in lung function and airway inflammation as measured by exhaled nitric oxide, a blood eosinophil count or other measures of TH2 like inflammatory responses. Increased number of eosinophils in the airway and blood are found in asthma reflecting a Th2 pattern of inflammation which leads to the production of increased amounts of a cytokine called IL-5 which is a specific growth factor for eosinophils. IL-5 is released by Th2 lymphocytes and a new described class of innate cells called innate lymphoid cells type 2. In most patients with asthma the allergic response results in increased amounts of specific IgE. However in a significant proportion of asthmatics particularly those with adult-onset asthma the eosinophilia occur without increased IgE. The mechanism driving this inflammatory process in this group of patients is not clear although the likelihood is that it is a non-IgE-mediated ILC2 mediated process driven by environmental stimuli and by IL-5 which is inhibited by reslizumab. The degree of eosinophilia associated with asthma varies considerably with a proportion of patients including those of adult-onset having a marked blood and tissue eosinophilia. It is likely these patients will respond to reslizumab.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Eosinophilic asthma is the mechanism associated with the most severe form of asthma and the most difficult to treat. A high proportion of

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Single Technology Appraisal (STA)

those requiring ventilation have eosinophilic asthama. The National Review of Asthma Deaths established that at least 15% of those who died from asthma had evidence of eosinophilia and this is likely to be an underestimate.

Reslizumab is effective in preventing severe exacerbations in people with eosinophilic airway disease. The more eosinophilic they are the more they will benefit. Eosinophilic inflammation is often disconnected from the traditional symptom pattern of asthma (it can be clinically silent for periods of time), and the physiological abnormalities associated with asthma. The indications for the use of reslizumab have to reflect the pattern of asthma where it will be of most benefit and should include people with an exacerbation prone endotype who may not necessarily demonstrate typical asthma symptoms or variable airflow obstruction. It is critical therefore that severe eosinophilic asthma is broadly defined as people with severe exacerbation prone eosinophilic airway disease as measured by exhaled Nitric oxide and/or sputum and/or blood eosinophilia.

In the majority, eosinophilic inflammation can be prevented by inhaled steroids and treatment failure may be due to sub-optimal adherence. While it is reasonable for reslizumab to be used as an alternative to regular oral steroids it will be essential to objectively establish that patients are compliant with their inhaled treatment before reslizumab is considered .

Because of high cost of this technology it is most appropriate for reslizumab to be initiated and monitored in tertiary care.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

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Single Technology Appraisal (STA)

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The delivery of reslizumab will require new infrastructure because it is delivered intravenously. Administration will likely take place in day wards and the patient admitted as a day case.

The evidence base suggests that response will depend on careful selection of patients. Those with an eosinophilic driver to their asthma will benefit but not other asthma patients even if they have severe disease. Therefore considerable expertise will be required to select appropriate patients for this technology ensuring that they have the clinical features compatible with eospinophilic asthma backed up with direct evidence of airway eosinophilia (bronchial biopsy or induced sputum) or indirect evidence (blood count eosinophilia, elevated exhaled nitric oxide).

From published studies it is likely that response to treatment may require a trial of treatment of 4 months and using the model already established for omalizumab – treatment can either be stopped or continued with annual reviews of response undertaken.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

N/A

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Single Technology Appraisal (STA)

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Some additional infrastructure and staffing may be required however overall it is likely that targeted use of reslizumab will reduce exacerbations of severe asthma and hence hospital admission. Therefore resource can be redirected to be more out-patient focussed and preventative rather than reactive. This will benefit patients and improve quality of life.

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Patient/carer expert statement (STA)

Reslizumab for treating eosinophilic asthma inadequately controlled on inhaled corticosteroids [ID872]]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: XXXXXXXXXXX
Name of your nominating organisation:
Do you know if your nominating organisation has submitted a statement?

x☐ Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

x☐ Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

☐x Yes ☐ No

- a carer of a patient with the condition?

☐ Yes ☐ No

- a patient organisation employee or volunteer?

☐ Yes ☐ No

Do you have experience of the treatment being appraised?

☐ Yes ☐ No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

My experience has been life changing since being diagnosed not only for me but also my family. I personally have lost my employment because of asthma due too unable to carry out everyday tasks for example washing my hair, dressing. Prior to the asthma I was playing sports at a county level, now a good day is managing to walk a few paces. My social life evaporated due to spending so much time in hospital and unable to participate in everyday activities. For e. g going for a coffee with friends. My parents also have had to take numerous time of work resulting in a lower income for them making therefore they are now financially worse as having to care for me and take me to appointments.

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

From a personal point any treatment which relieves symptoms without the horrendous side effects. Unfortunately, the permanent use of steroids has caused myself, eye problems, type 2 diabetes, chronic kidney disease to name just a few which then need more medication and hospital time to manage and treat. A treatment which allowed the use of steroids to be lowered completely would be warmly welcomed to end the vicious cycle of taking immense amounts medication for aliments caused by the steroids for example the diabetes. In turn allowing me to participate fully in life again.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

Quality of life, Level of disability, independence, other people, improving the condition to a point where less medication is needed, hope to gain employment again in the future, improvement in physical and mental health.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

Would allow the use of steroids to be lowered and therefore the amount of drug treatment needed to manage side effects of such a high dose of steroids to be impacted positively.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

Please list any concerns you have about the treatment being appraised.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

Patients who like myself whom have exhausted all avenues of treatment and the side effect of current treatments are having a severe impact on their lives as well as the addition of asthma.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Is there anything else that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Would improve patient's quality of life
- Would allow the paitent to lower steroid medication
- Would allow paitent to take less medication due to severe side effects of the current medication on offer, therefore in the long term would be value for money.
-
-
-

CONFIDENTIAL UNTIL PUBLISHED

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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This version of the report includes corrections made by the ERG following the company's factual inaccuracy check. These are indicated as *underlined italicised text*.

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Declared competing interests of the authors

None

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We also thank Professor Joanne Lord, Director, SHTAC, for acting as internal editor for the draft report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Keith Cooper (Senior Research Fellow) critically appraised the health economic systematic review, critically appraised the economic evaluation and drafted the report. Petra Harris (Research Fellow) critically appraised the clinical effectiveness systematic review and drafted the report. Micah Rose (Research Fellow) critically appraised the health economic systematic

review, critically appraised the economic evaluation and drafted the report. Maria Chorozoglou (Senior Research Fellow) critically appraised the economic evaluation and drafted the report. Karen Pickett (Research Fellow) critically appraised the clinical effectiveness systematic review and drafted the report. Geoff Frampton (Senior Research Fellow) critically appraised the clinical effectiveness systematic review, drafted the report, project managed the review and is the project guarantor.

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[redacted].

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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.

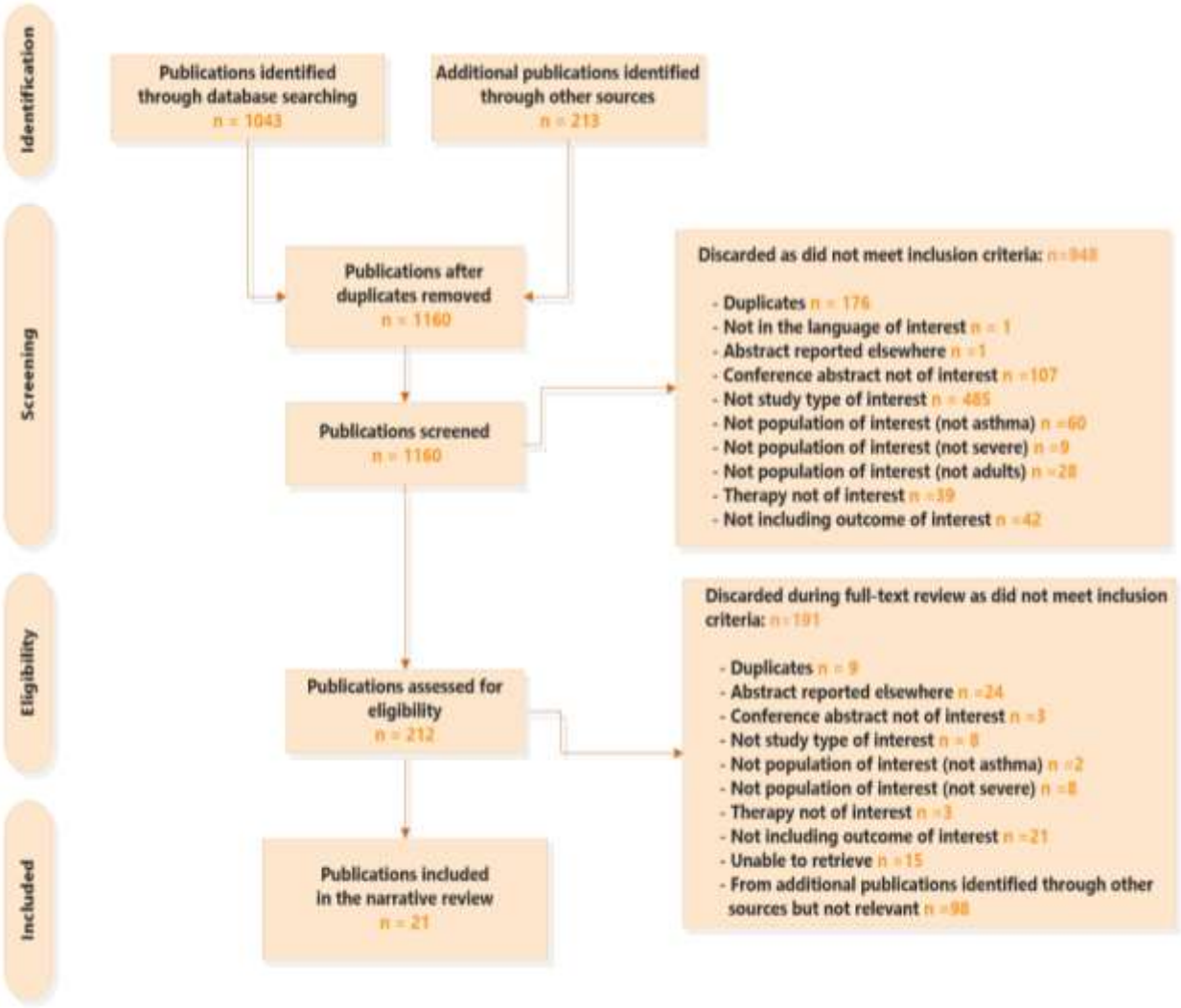


Figure 1 PRISMA diagram for the systematic review of clinical evidence

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* except*ion* 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).

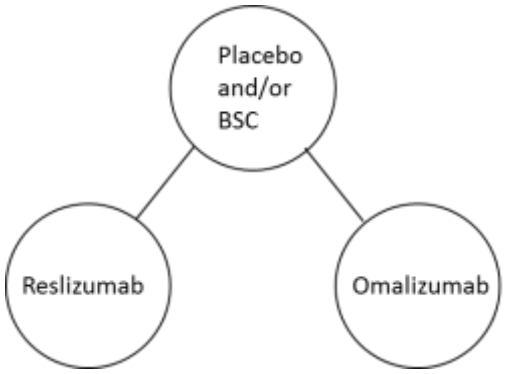


Figure 2 ITC network diagram

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.

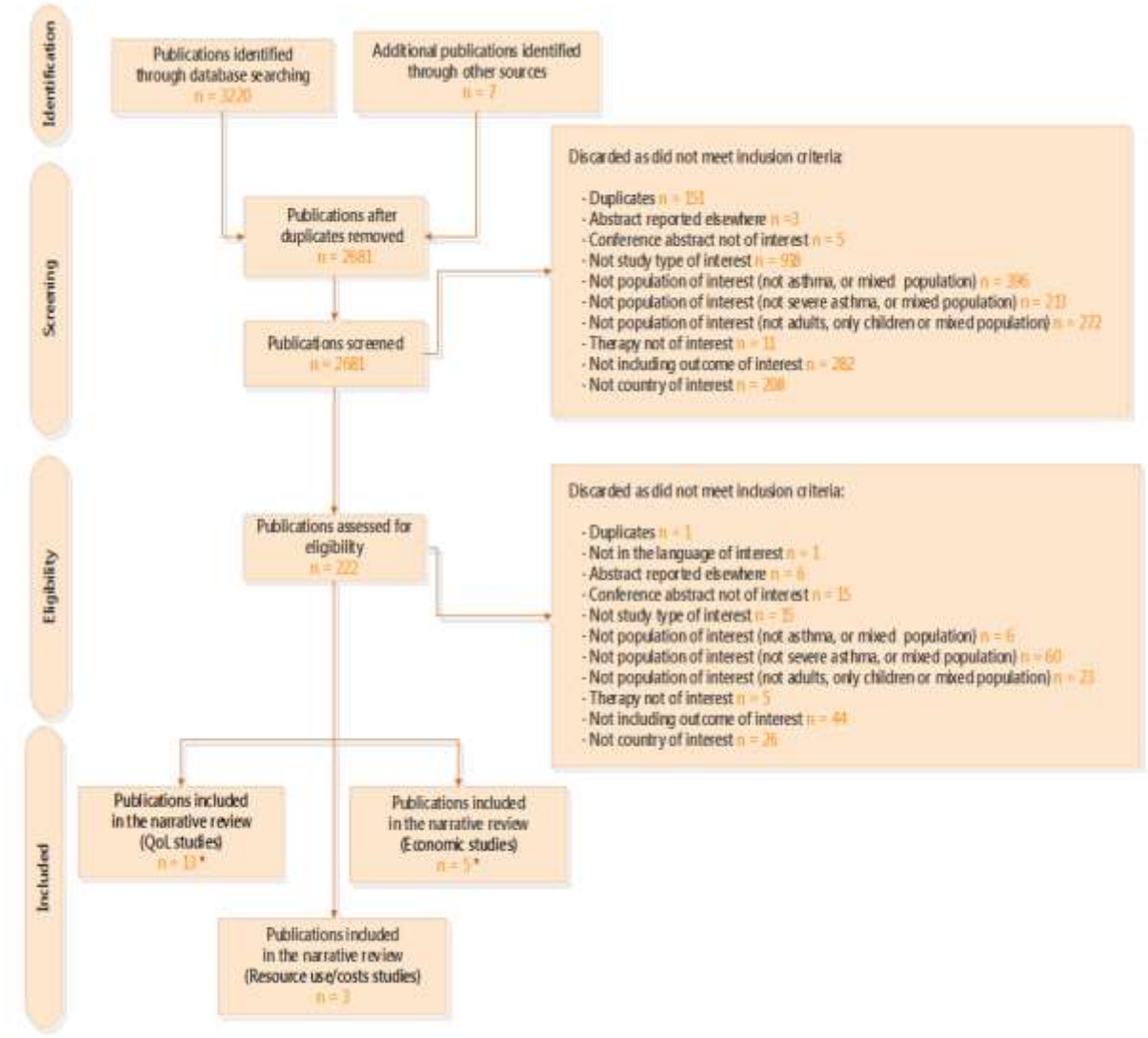


Figure 5 Flow diagram for the review of cost-effectiveness, HRQoL and healthcare resource use evidence

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.

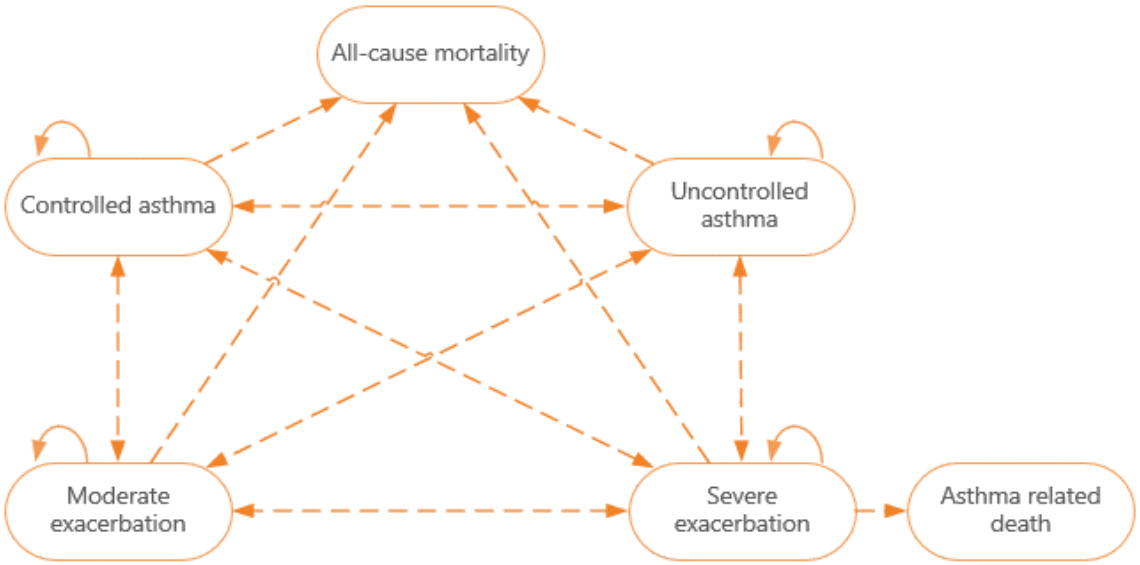


Figure 6 Schematic of company's model structure

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]

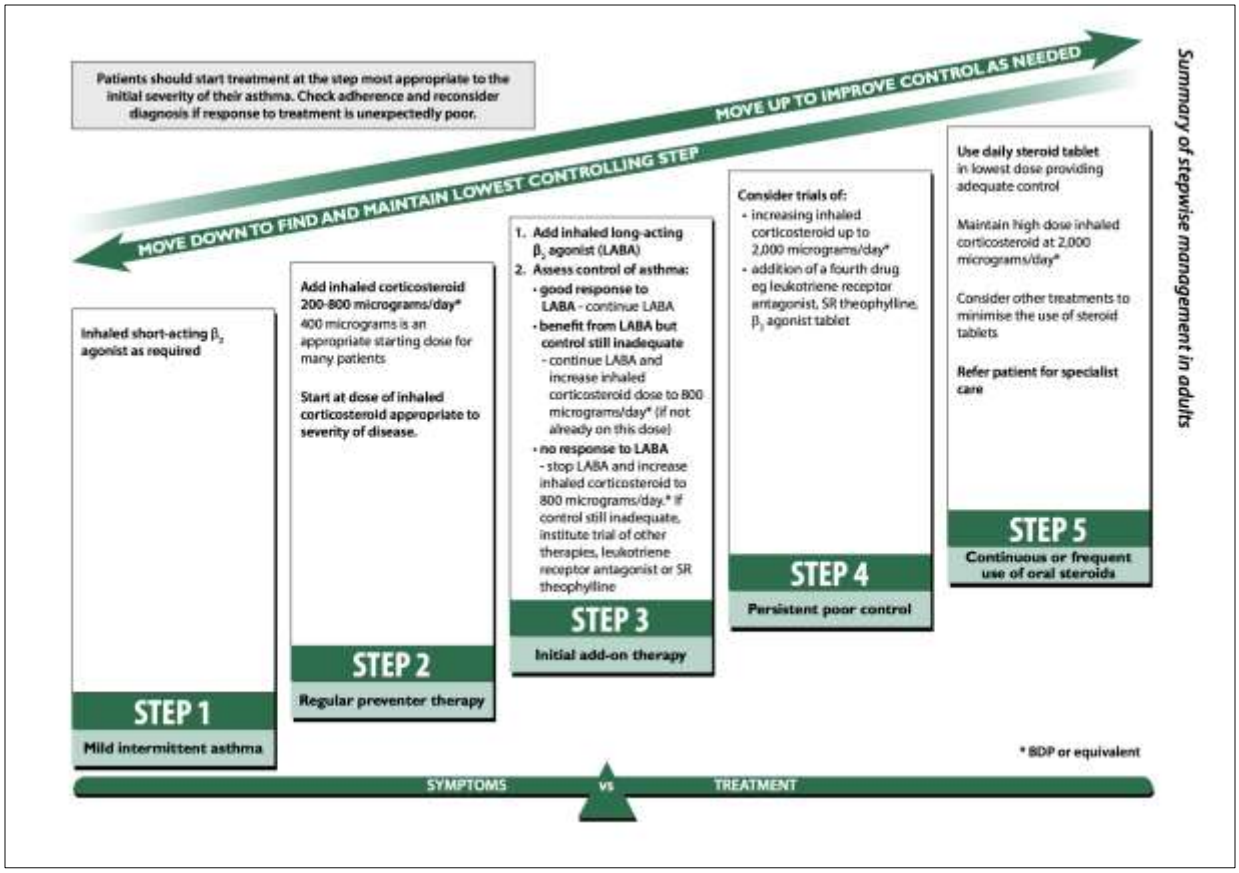
In the model, patients identified as non-responders transfer to the BSC treatment arm and then observe the BSC transition probabilities and costs for the remainder of the time horizon. Other patients (responders and those with an undetermined response status) are assumed to continue treatment beyond 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-

lgE antibody, recommended by NICE (TA278) as an option for treating severe persistent confirmed allergic lgE-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~~*T*he 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]	[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.

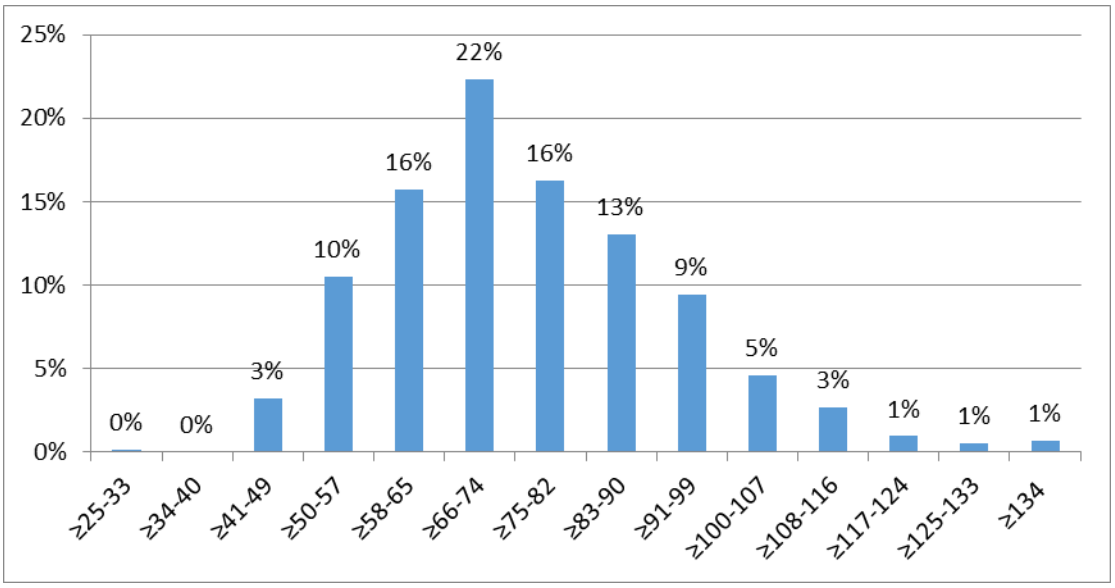


Figure 8 Weight distribution in kg – adult patients at GINA Step 4/5 enrolled in trials 3082 and 3083

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.

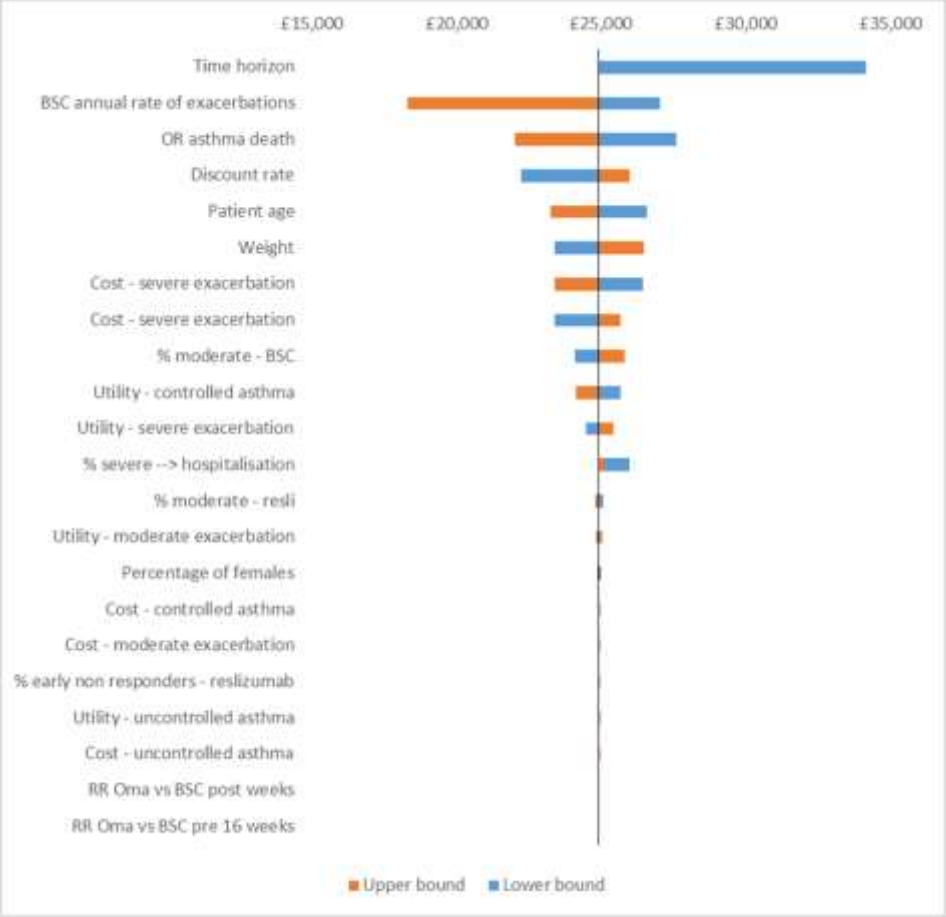


Figure 9 Tornado diagram: deterministic sensitivity of resilzumab vs BSC

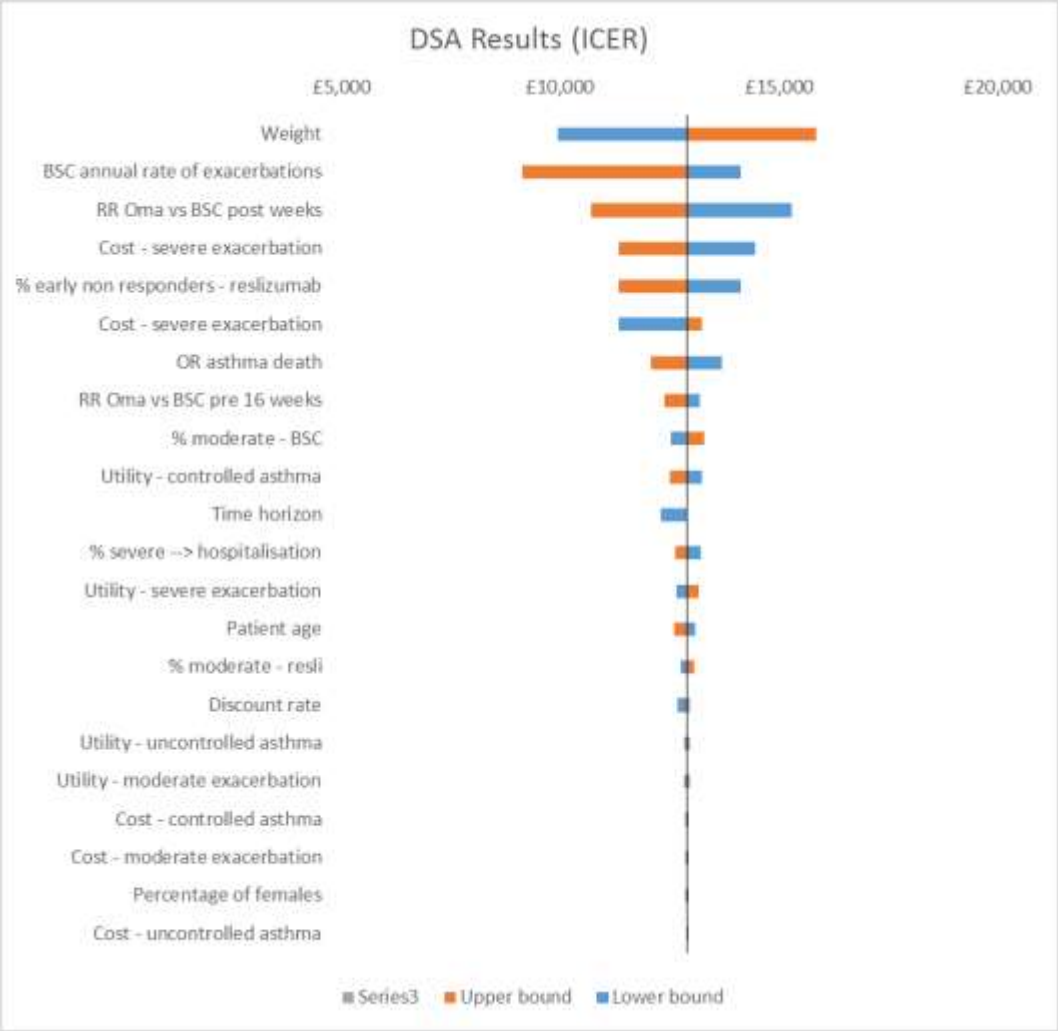


Figure 10 Tornado diagram: deterministic sensitivity of resilzumab vs omalizumab (from company's revised model)

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 .

[redacted] [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

Description of problem	Description of proposed amendment			Justification for amendment	ERG response
Incorrect section/page/table numbers in the CS cited.	ERG page number	Citation	Correction	Cited section/page/table numbers in the CS are inaccurate.	These cross-references have been corrected (pages 62, 82, 153, 163).
	61	(CS page 49)	(CS Section 4.9) ***or*** (CS page 135)		
	Table 24	Source: CS Tables 58 & 59	Source: CS Tables 58 & 60		
	Table 88	(CS Table 117, p205)	(CS Table 117, p206)		
	165	CS Tables 131 and 131	CS Tables 131 and 132		

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).