For Public

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

1st Appraisal Committee meeting

Cost Effectiveness

Committee A

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Key issues: cost effectiveness (1)

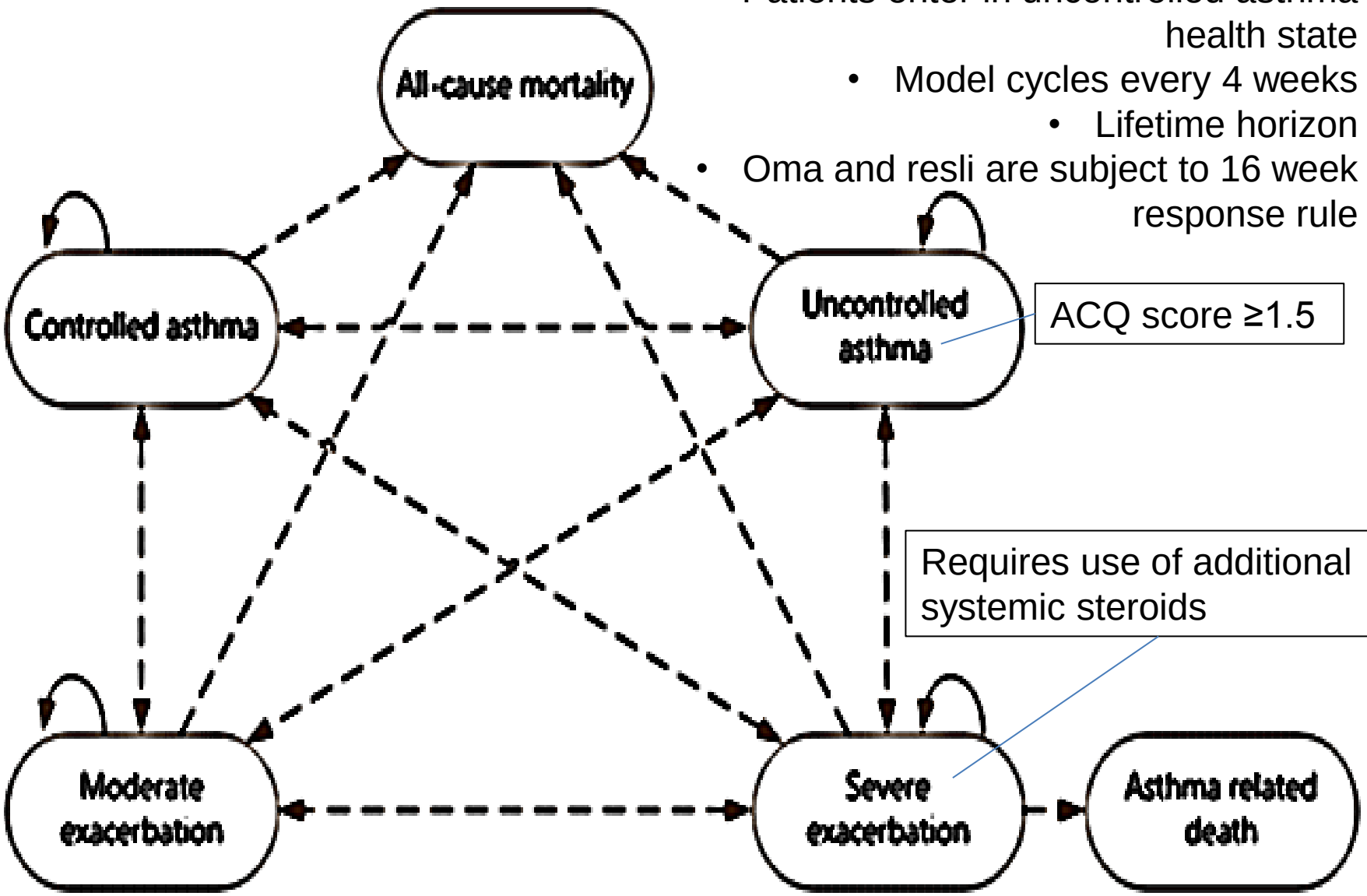
- The company used a subgroup of patients with 3 or more exacerbations in the previous year as the base-case; is this appropriate?
- The company applied a multiplier when calculating the transition probabilities in both the BSC and reslizumab arms to:
  - adjust the baseline risk of exacerbations for different subgroups.
  - adjust for a potential placebo effect.
- The ERG had concerns over the rationale for adjusting for a placebo effect, and how this was done. What is the committee's view?

Key issues: cost effectiveness (2)

- The company model includes two stopping rules, one at 16 weeks and one at 52 weeks. Are these appropriate?
- 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?

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 choosing 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 effects of reslizumab vs BSC	varied	Taken directly from 3082 and 3083

Transition probabilities

- Computed using patient level data from the 2 pivotal reslizumab clinical trials (studies 3082 and 3083).
  - subgroup of adults GINA 4/5 with ≥ 2 exacerbations in previous year.
  - company did not consider the subgroup with ≥ 3 exacerbations in previous year to be large enough for estimation of transition probabilites.

- A multiplier was used to:
  - adjust the baseline risk of exacerbations for different subgroups (all adults, those with ≥ 2, ≥ 3, ≥ 4 exacerbations in previous year).
  - correct for a potential placebo effect, by calibrating the model to produce observed rate of exacerbations in the year prior to randomisation in those randomised to placebo.

Exacerbation multiplier

Mean annual rates of exacerbations in placebo arms (studies 3082 and 3083)				
Subpopulation	**N ***	**Year prior to random-isation**	**Year after random-isation**	**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	[redacted]	1.59
Adults; GINA Step 4 and 5, ≥3 exacerbations in the preceding year	158	[redacted]	2.73	[redacted]
Adults; GINA Step 4 and 5, ≥4 exacerbations in the preceding year	94	5.81	2.88	2.62

ERG table 68, pg. 127

Multiplier applied to both BSC and reslizumab arms in the economic model, to retain relative treatment effects estimated in the clinical trials.

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ERG comments on company's adjustment of transition probabilities

- Adjusting for different levels of baseline risk in subgroups is appropriate, but base case should reflect observed risk in trial populations.
- Unconventional but not unreasonable to correct placebo estimates for placebo effect. Unclear why reslizumab arm should also be corrected for a placebo effect.
- More appropriate to model BSC arm with an absolute risk and then multiply by relative risk (from trial) to obtain absolute risk in reslizumab arm.
- Lower rate of exacerbations in year after randomisation may not be due to a placebo effect. Could be at least partly a result of "regression to the mean".

Other issues with company's adjustment of transition probabilities

- Multiplier is based on ratios of mean rates of exacerbations which are estimated with uncertainty, so multiplier will also be associated with considerable uncertainty.
- Unclear why the pre-trial exacerbation rates were only estimated in those subsequently randomised to placebo, rather than using data from all individuals in the relevant subgroup, which would have given larger samples and therefore more precise estimates.
- Adjustment for placebo effect only applied to transition probabilities for exacerbation health states
- Do the resulting transition probabilities accurately reflect clinical experience?

Transition probabilities

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

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

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

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Reslizumab	[redacted] per 100 mg vial	Teva UK Limited, PAS price
Reslizumab	[redacted] per 25 mg vial	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
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 no hospital: £234.21 Severe exacerbation no hospital: £1,906.54	

Company's base case deterministic results

using PAS price for reslizumab and list prices for BSC for omalizumab

Treatment arm	Total		Incremental ICER/QALYs	ICER/ QALYs, £ vs BSC
	Costs, £	QALYs		
Company's base case: Patients with a history of ≥3 exacerbations				
BSC	[redacted]	[redacted]		
Reslizumab	[redacted]	[redacted]	£24,907	£24,907
Patients with severe persistent allergic IgE-mediated eosinophilic asthma and a history of ≥3 exacerbations				
BSC	[redacted]	[redacted]		
Omalizumab	[redacted]	[redacted]	Extendedly dominated	£37,917
Reslizumab	[redacted]	[redacted]	£24,907	£24,907

Probabilistic ICER were similar to the deterministic ICERs

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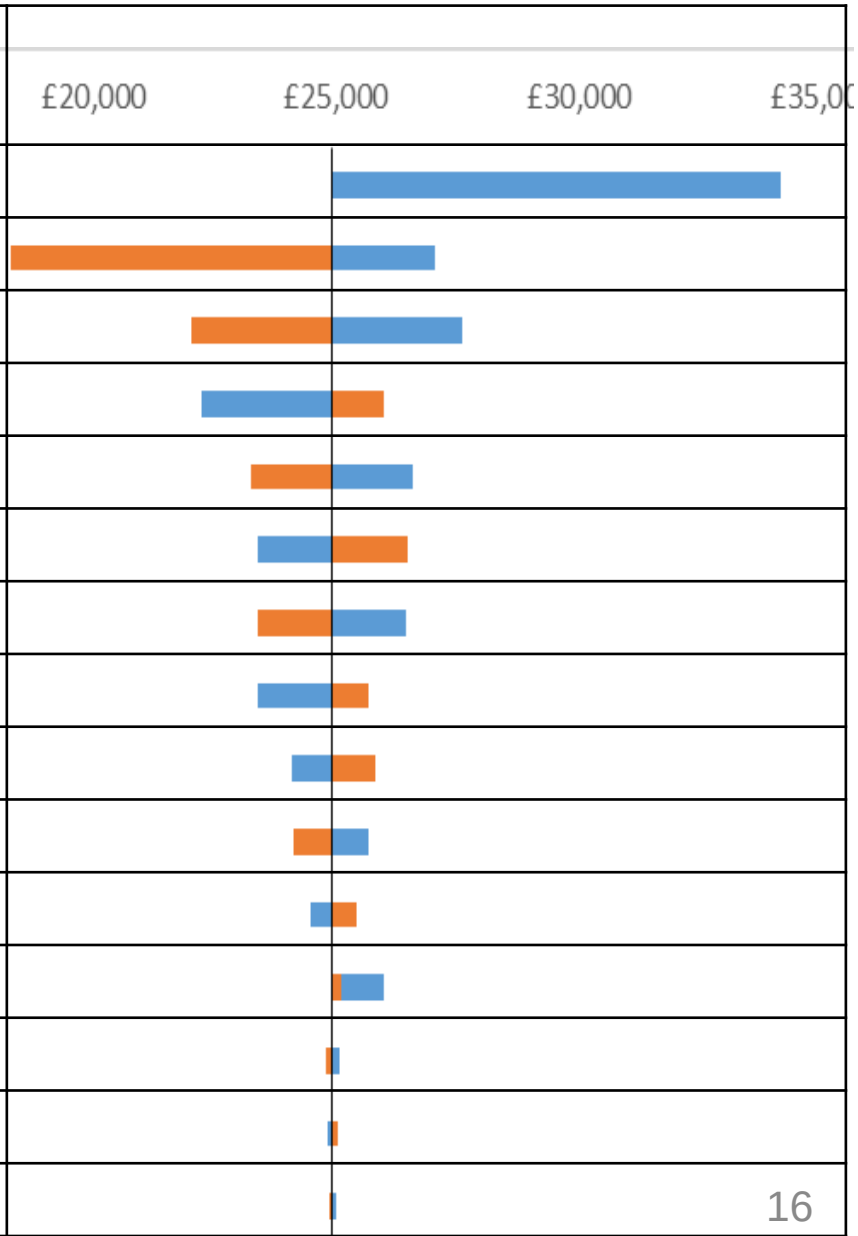
Tornado diagram

(reslizumab PAS vs list price BSC)

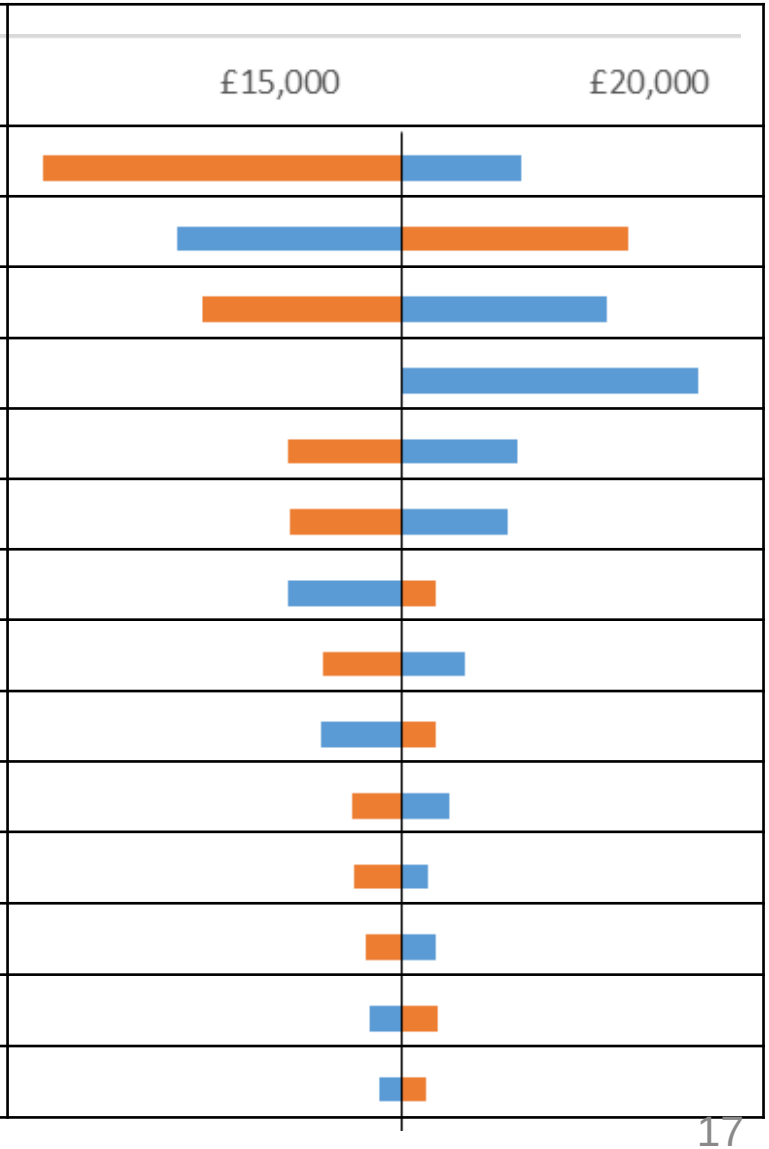
Base Case	Min - Max	
60 yrs	5 - 60	Time horizon
4.67	4.29 – 5.05	Ann. rate of exacer. BSC
Varied by age		OR asthma death
3.5	0 – 5%	Discount rate
46.8	37.4 -56.2	Patient age
9.58	9.08 -10.08	Weight (number of vials)
£649	£520 - 779	Cost – severe exacer.
£649	£520 - 779	Cost – severe exacer.
18.2%	14.6 - 21.6	% moderate - BSC
0.92	0.90 - 0.94	Utility – controlled asthma
0.33	0.31 - 0.35	Utility – severe exacer.
24.8%	19.9 - 29.8	% severe - > hospitalised
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 PAS vs omalizumab list price)

Base Case	Min - Max	
4.67	4.29 - 5.05	Ann. rate of exacer. BSC
9.58	9.08 - 10.08	Weight (number of vials)
0.82	0.41 - 1.61	RR oma vs BSC post weeks
60 yrs	5 - 60	Time horizon
£649	£520 - 779	Cost – severe exacer.
Varied by age		OR asthma death
£649	£520 - 779	Cost – severe exacer.
13.2%	8.2 - 18.2	Early non-responders – resli.
3.5	0 – 5%	Discount rate
46.8	37.4 -56.2	Patient age
0.37	0.27 - 0.52	RR oma vs BSC pre 16 wks
0.92	0.90 - 0.94	Utility – controlled asthma
18.2%	14.6 - 21.6	% moderate - BSC
0.33	0.31 - 0.35	Utility – severe exacer.



Company's subgroup analyses

using reslizumab PAS and list price for BSC

Treatment arm	Total		ICER/ QALY, £ vs. BSC
	Costs, £	QALYs	
Company's base case: Patients with a history of ≥3 exacerbations			
BSC	[redacted]	[redacted]	
Reslizumab	[redacted]	[redacted]	£24,907
Patients having experienced ≥2 exacerbations			
BSC	[redacted]	[redacted]	
Reslizumab	[redacted]	[redacted]	£33,774
Patients having experienced ≥4 exacerbations			
BSC	[redacted]	[redacted]	
Reslizumab	[redacted]	[redacted]	£20,006

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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

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ERG's exploratory analyses - changes to exacerbation multiplier

using reslizumab PAS and list prices for BSC and omalizumab

Scenario	Treatment	Total		Incremental ICER (£/QALY)
		Costs, £	QALYs	
Company's base case, Patients with ≥2 exacerbations in previous year, multiplier = 2.15	BSC	[redacted]	[redacted]	
	Omalizumab	[redacted]	[redacted]	Extendedly dominated
	Reslizumab	[redacted]	[redacted]	£24,907
ERG's analysis, Patients with ≥2 exacerbations in previous year, multiplier = 1)	BSC	[redacted]	[redacted]	
	Omalizumab	[redacted]	[redacted]	Extendedly dominated
	Reslizumab	[redacted]	[redacted]	£50,878

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ERG's exploratory analyses –

utility values, reslizumab PAS and list prices for BSC and omalizumab

Health State	Ratio to baseline	Base case	Utility Scenario 1	Utility Scenario 2	Utility scenario 3
Uncontrolled	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	Incremental ICER (£/QALY)
Company 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

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 reslizumab PAS and list prices for BSC and omalizumab

Contains CIC

Scenario	Treatment	Total		Incremental ICER (£/QALY)
		Costs, £	QALYs	
Company's base case	BSC	[redacted]	[redacted]	
	Omalizumab	[redacted]	[redacted]	Extendedly dominated
	Reslizumab	[redacted]	[redacted]	£24,907
ERG's preferred base case	BSC	[redacted]	[redacted]	
	Omalizumab	[redacted]	[redacted]	Extendedly dominated
	Reslizumab	[redacted]	[redacted]	£57,356

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 used a subgroup of patients with 3 or more exacerbations in the previous year as the base-case; is this appropriate?
- The company applied a multiplier when calculating the transition probabilities in both the BSC and reslizumab arms to:
  - adjust the baseline risk of exacerbations for different subgroups.
  - adjust for a potential placebo effect.
- The ERG had concerns over the rationale for adjusting for a placebo effect, and how this was done. What is the committee's view?

Key issues: cost effectiveness (2)

- The company model includes two stopping rules, one at 16 weeks and one at 52 weeks. Are these appropriate?
- 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?