For public handouts

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

1st Appraisal Committee meeting

Clinical Effectiveness and Patient/Carer Perspective

Lead Team

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Key issues: clinical effectiveness (1)

- Is the clinical effectiveness data from the trials generalisable?
- In the studies an eosinophil count of ≥400 cells/μL was used to define ‘asthma with elevated eosinophils’. What definition is used in clinical practice?
- Patients in the clinical trials used moderate to high dose inhaled corticosteroids and low rates of oral corticosteroids. Is this an appropriate group to study?
- Patients were eligible for the studies if they had two or more exacerbations of asthma in the previous year. Is this considered to be ‘inadequately controlled asthma’?

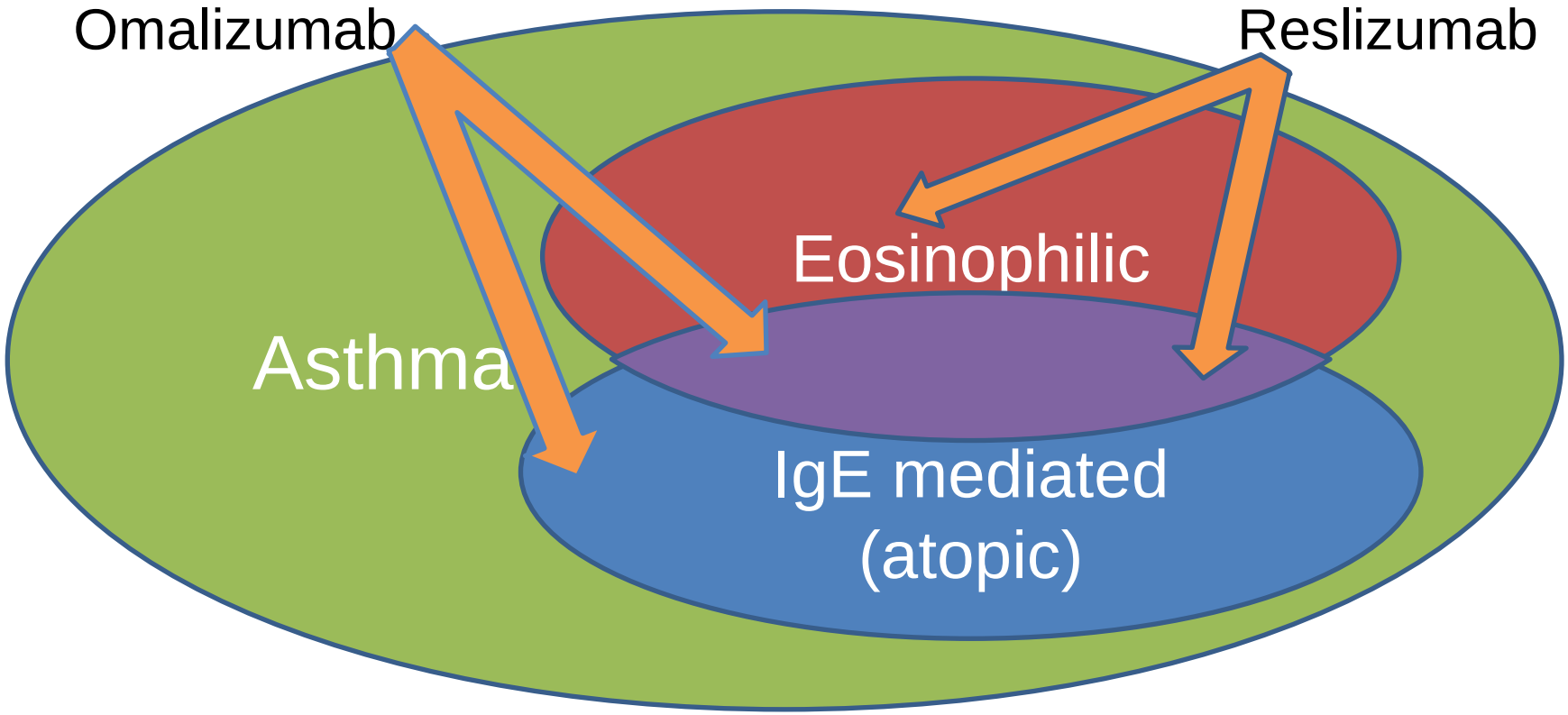
Key issues: clinical effectiveness (2)

- Data are only available for up to 52 weeks from the trials: would the benefit continue longer term?
- Placebo was the comparator in the trials. What would be the alternative treatments for these patients in clinical practice?
  - Might they include higher dose inhaled steroids, oral corticosteroids, mepolizumab or omalizumab?
- Improvement in the placebo arm was seen in the trial – what is the significance of this?
- In patients with both eosinophilia and IgE mediated asthma, where omalizumab might be used, how reliable is the ITC comparing reslizumab with omalizumab?

Disease Background

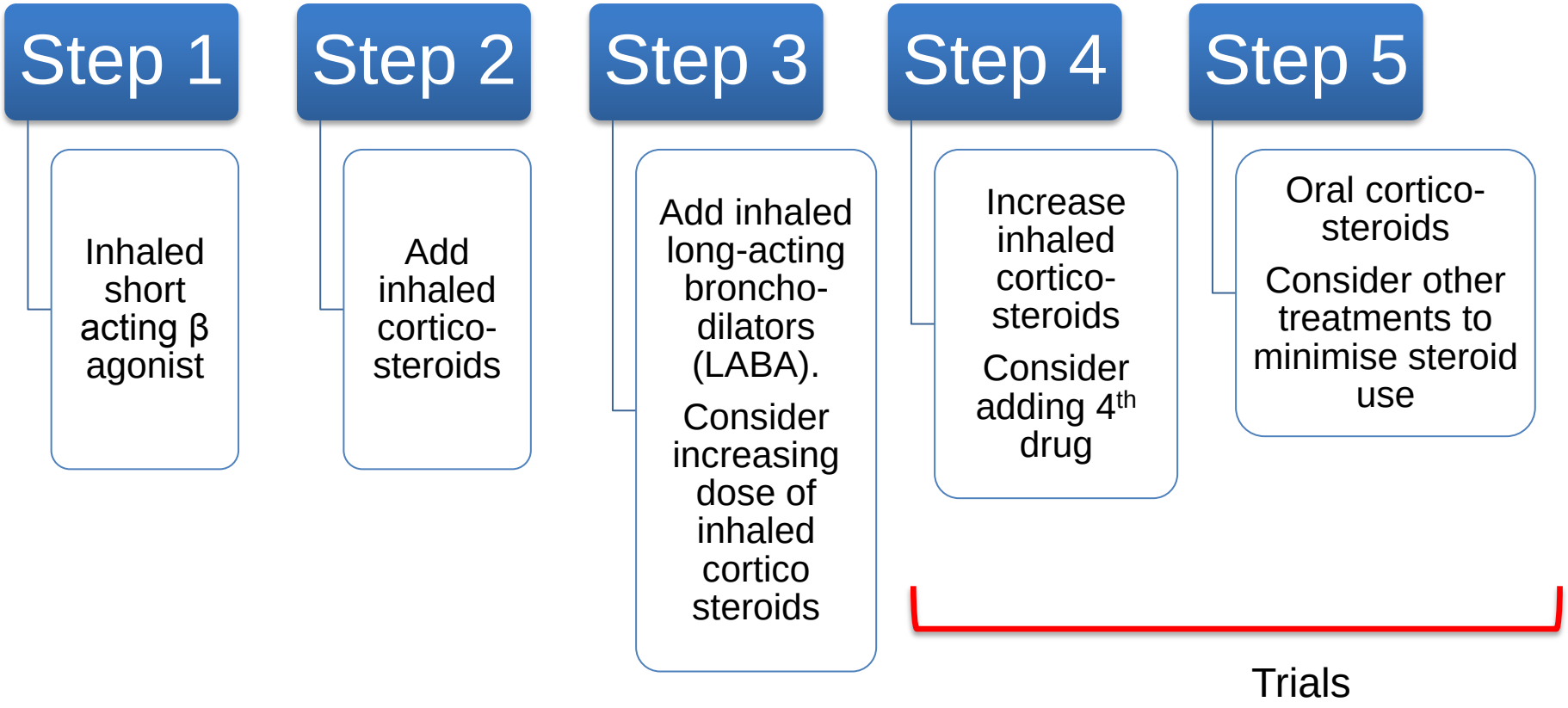
- Asthma is a disease of airway inflammation with associated airflow limitation and hyper responsiveness to intrinsic and extrinsic stimuli
- 5.4 million people in England and Wales receive treatment for asthma
- In 2014, there were 1,133 asthma related deaths in the UK
- 5-10% people have severe asthma
- Severe asthma is 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	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 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 agonist 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 a 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

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 corticosteroids 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

Reslizumab clinical studies

Name	Inclusion criteria	Intervention	Comparator	No. pts	**Duration**
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	489	52 weeks
Study 3083				464	
Study 3081		Reslizumab 0.3 mg/kg; **Reslizumab 3.0 mg/kg**	Placebo	315	16 weeks

Studies 3082 and 3083 provide the core efficacy evidence.
3082, 3083, and 3081 included patients aged 12-75 years (although mean age from main trials was 44-47 years)
No UK centres for 3082, 3083 or 3081

Additional reslizumab studies

Name	Inclusion criteria	Intervention	Com-parator	Duration
Study 3084	Adult patients with moderate to severe asthma uncontrolled with medium to high dose ICS	Reslizumab 3.0 mg/kg	Placebo	16 weeks
Study 3085	Open label extension study of 3081, 3082 and 3083			Up to 24 months
Phase II studies				
Res-5-0010	Adult patients (18-75 years) with poorly controlled asthma and eosinophilic airway inflammation (sputum eosinophils ≥3%)	Reslizumab 3.0 mg/kg	Placebo	15 weeks

Outcomes and direct meta-analysis of reslizumab vs placebo trials

- Clinical asthma exacerbations (Primary end-point)
- Lung Function (Change in FEV_1)
- Asthma control questionnaire (ACQ) score
- Health-related quality of life - Asthma Quality of Life Questionnaire (AQLQ)
- Meta-analysis:
  - 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 for clinical asthma exacerbations (reslizumab versus placebo)

Trial	Adjusted mean frequency		Rate ratio (95% CI)
	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
3083	0.86 (n=232)	2.11 (n=232)	0.41 (0.28, 0.59); p<0.0001
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
3083	[redacted]	[redacted]	[redacted]
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
3083	[redacted]	[redacted]	[redacted]

Direct comparison meta-analysis: clinically significant exacerbations

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

Results for changes in lung function (FEV1) (reslizumab vs placebo)

FEV_1: mean change from baseline (L) at 16±1 weeks			
Trial	**Reslizumab**	**Placebo**	**Mean difference (95% CI)**
3082	0.20 (n=232)	0.13 (n=228)	0.07 (0.001, 0.14); p=0.0483
3083	0.25 (n=214)	0.15 (n=214)	0.10 (0.02, 0.18); p=0.0109
3081	0.24 (n=91)	0.05 (n=84)	0.17 (0.04, 0.29); p=0.0118
FEV_1: mean change from baseline (L) at 52 week			
3082	0.24 (n=243)	0.08 (n=241)	Not reported
3083	0.23 (n=230)	0.12 (n=227)	Not reported

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

ACQ score: mean change from baseline at 16±1 weeks			
Trial	**Reslizumab**	**Placebo**	**Mean difference (95% CI)**
3082	-0.94 (n=242)	-0.68 (n=241)	-0.27 (-0.40, -0.13); p=0.0001
3083	-0.86 (n=230)	-0.66 (n=228)	-0.20 (-0.33, -0.07); p=0.0032
3081	-0.94 (n=91)	-0.58 (n=84)	-0.35 (-0.63, 0.08); p=0.0129

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

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)
3082	1.03 (n=228)	0.87 (n=229)	0.24 (0.05, 0.43); p=0.0143
3083	0.95 (n=213)	0.79 (n=216)	0.21 (0.03, 0.39); p=0.0259
3081	1.14 (n=99)	0.78 (n=101)	0.36 (0.05, 0.67); p=0.0241
AQLQ score: mean change from baseline at 52 weeks			
3082	1.30 (n=245)	1.01 (n=244)	Not reported
3083	1.10 (n=232)	0.90 (n=232)	Not reported

Direct comparison meta-analysis: AQLQ score changes over 16 and 52 weeks		
	Difference between means, reslizumab versus placebo (95% CI)	
	16 weeks	52 weeks
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

- Most common AEs (>20%):
  - asthma,
  - upper respiratory tract infection,
  - nasopharyngitis,
  - sinusitis,
  - headache,
  - influenza
  - bronchitis
- 5% of treatment related adverse events were moderate or severe
- No significant difference in adverse events between reslizumab or placebo arms

ERG comments

- Included trials are of generally high quality
- Trials had relatively short duration (52 weeks maximum – 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.

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