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

2nd Appraisal Committee meeting

11th January 2017

Slides for public

Issues for committee

- Is ≥400/μL blood eosinophil count (as in the trials) a recognised criterion for the diagnosis of eosinophilic asthma in the UK?
- How generalisable is the trial considering the small proportion of patients in the trial that were taking oral corticosteroids at baseline? (12%-19%)
- Is the committee satisfied that a steroid sparing effect has been captured in the evidence?
- Is the committee minded to accept that clinical need is higher in patients with ≥4 exacerbations in the preceding year compared to patients with ≥3 exacerbations in the preceding year?
- Is the committee prepared to accept the “real world data” adjustment to the BSC arm in the trial which has now been suggested by the company as best representing the expected exacerbation rate in clinical practice?
- Is the committee minded to accept the company’s cost-effectiveness analysis based on the 25 mg vial (instead of the 100 mg vial as requested)

ACD preliminary recommendations additional data requested

- Committee preferred a model that used the observed (unadjusted) data from the relevant subgroup in the trials to determine the transition probabilities. A multiplier may be reasonable, but only to adjust for different levels of baseline risk in each subgroup and not to adjust for a possible placebo effect
- The effect of reslizumab on exacerbations for subgroups of people with 3 or more or with 4 or more exacerbations in the previous year. These should not include an adjustment for a placebo effect
- Appropriate administration costs, including the need to go to hospital for infusion, and drug wastage using only the licensed 100-mg vial
- Evaluation of response to treatment at periods that reflect clinical practice (such as 6 months from the start of treatment)
- The individual and combined effects of all amendments on the incremental cost-effectiveness ratios (ICERs) for adults with inadequately controlled severe eosinophilic asthma despite optimised best standard care at specialist centres.
- Committee recommends that the company also considers how reslizumab may affect oral corticosteroid usage and its consequent adverse effects and their costs.

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

Oral corticosteroid use: 19%(study 3082), 12% (study 3083), 0 (study 3081)

Transition probabilities

- Computed using patient level data from 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 probabilities.
- 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.
  - Multiplier applied to both BSC and reslizumab arms in the economic model, to retain relative treatment effects estimated in the clinical trials.

Committee conclusions

- Inadequately controlled severe eosinophilic asthma is associated with substantial morbidity – need for alternative treatment options.
- In clinical practice, patients considered for this treatment may have lower eosinophil counts than in the trials and a higher percentage will be on oral corticosteroids.
- A criterion based on the number of exacerbations is not unreasonable: the more frequent the exacerbations, the greater the clinical need.
- Reslizumab may be considered for people who are not taking maintenance oral corticosteroids but it would be most beneficial for people who have multiple exacerbations despite maintenance oral corticosteroid use.
- Reslizumab is effective in reducing the rate of clinically significant exacerbations compared with placebo.
- As more patients in UK clinical practice have maintenance oral corticosteroids than those in the trials, it would be reasonable for the company to explore what impact reslizumab might have on oral corticosteroid usage and its related adverse effects and costs.

Consultation comments

- The following organisations responded:
  - Asthma UK
  - British Thoracic Society
  - NHS England
  - Novartis
  - Royal College of Physicians
  - Teva
- Comments also received from one of the clinical experts

Consultation issues (1) – mepolizumab

- Why isn't resilizumab compared to mepolizumab? (BTS and RCP)
  - BTS notes that two ongoing trials will have data available by 2018 allowing comparison, as well as more real life data
  - RCP notes that both drugs are monoclonal antibodies that will be used for the same group of patients and expressed concern that both will be used interchangeably.
- Can wording in reslizumab guidance mirror mepolizumab guidance i.e. consistency in number of exacerbations and in the eosinophilic levels required to be eligible for treatments? (NHS England)
  - Consistency in the eosinophilic levels required to be eligible for treatments required. Different levels set by Committee A and B in the appraisals of reslizumab and mepolizumab.

Mepolizumab FAD

1.1 Mepolizumab, as an add-on to optimised standard therapy, is recommended as an option for treating severe refractory eosinophilic asthma in adults, only if:

- The blood eosinophil count is 300 cells/microlitre or more in the previous 12 months
- The person has agreed to and followed the optimised standard treatment plan and:
  - The person has had 4 or more asthma exacerbations needing systemic corticosteroids in the previous 12 months or
  - The person has had continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months […]

Stopping rule:

1.2 At 12 months of treatment:

- stop mepolizumab if the asthma has not responded adequately or
- continue treatment if the asthma has responded adequately and assess response each year (adequate response defined in FAD)

Mepolizumab FAD evidence base

- Data mainly from 3 RCTs in patients with:
  - Severe refractory eosinophilic asthma on high-dose oral corticosteroids and a history of 2 or more exacerbations in the previous 12 months.
  - Blood eosinophil level of either 300 cells/microlitre or more in the 12 months before screening or 150 cells/microlitre or more at screening.
  - One trial (SIRIUS, n=135) included people with asthma who needed regular treatment with maintenance systemic (oral or injectable) corticosteroids and high-dose inhaled corticosteroids.
- Clinical experts agreed that:
  - Population based on a blood eosinophil count of 300 cells/microlitre or more in the previous 12 months would be relevant to clinical practice.
  - Criterion based on 4 or more exacerbations per year would identify the most severe patient group which would gain the most benefit.
  - Agreed that that population should be defined as in the SIRIUS trial, that is, having continuous OCS of at least the equivalent of prednisolone 5 mg/day in the 6 months before the start of treatment.

Consultation issues (2)

- Oral corticosteroids (OCS) (Asthma UK)
  - Trial (Sweeney et al.) identified presenting data from two large severe asthma populations from registries on burden of OCS and resulting co-morbidities.
- Administration costs used in model (Novartis)
  - Concerns raised regarding number of vials used being underestimated; current model assumes one vial (100mg) sufficient for patient weighing 40 kg (would require120mg).
  - Vial sharing with reference to shelf life of reslizumab from SmPC questioned
  - Timing assumptions for treatment preparation, administration and monitoring costs are not reflective of UK clinical practice or reslizumab SmPC.

Consultation issues (3)

- Evaluation of response (NHS England)
  - Omalizumab is assessed at 16 weeks and would be helpful to evaluate responses to new therapies at similar time points. Clinically plausible to use 16 week assessment in this patient population
- Eosinophil count (NHS England)
  - Assumption of UK patients with lower eosinophil count questioned as a recent trial demonstrated that at referral patients had a median eosinophil count of 300 with an interquartile range of 150-600 (Gibeon et al. Chest 2015) (NHS England)
- Specialist centre definition (RCP)
  - Care should be approved and monitored by regional MDTs and there should be registries run by the specialist centres to allow people access to local services.
  - Experts in accredited centres should use clear inclusion/exclusion criteria to identify patients with invasive (in comparison to benign) eosinophilia

Consultation issues (4) – diagnosis

- Diagnosis of eosinophilic asthma more straightforward and routine in specialist centres than suggested in ACD (clinical expert)
- Indications for reslizumab in people with severe eosinophilic asthma who have been optimized in specialized centres is should be either:
  - Poor control, despite optimized care in a specialist centre, with 3/4 or more severe exacerbations a year.
  - OR
  - Patients requiring oral corticosteroids irrespective of the number of exacerbations they have had in the previous 12 months (clinical expert)
- Any future positive recommendation should include blood eosinophil requirement and clear definition of eligible population (number of people with x number of exacerbation with definition of exacerbation based on reslizumab trials (Novartis)

Company response (1)

XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXX

Number of exacerbations in the previous year	n	Exacerbation rate reduction [adjusted rates Placebo versus Reslizumab]
≥3	158	XXXXXXXXXXX XXXXXXXXX
≥4	94	XXXXXXXXXXX XXXXXXXXX

Company response (2)

Transition probabilities

- Transition probabilities for reslizumab and BSC were estimated based on patients who had experienced 3 exacerbations or more (N=158) in both active and placebo arm combined.
- Transition matrix for smaller population (N=94) who experienced 4 or more exacerbations was estimated based on patients that experienced 3 exacerbations or more but adjusted for the incidence of exacerbations to reflect the mean rate of exacerbations observed in clinical practice for this specific subgroup

Rate of exacerbation in the BSC arm

- Rate of exacerbations in the BSC arm for cost-effectiveness analysis was estimated using real world data from a UK severe asthma registry. Real world evidence on exacerbation rates in the target population treated for severe asthma was used to account for baseline risk of exacerbations.

Company response (3) – 'real world' exacerbation rates

Study	Number of severe exacerbations in the year	Sample size	Mean number of severe exacerbations
XXXXXXX	≥1	XXX	XXX
XXXXXXX	≥3	XXX	XXX
XXXX	≥4	XXX	XXX
	≥1	XXX	XXX
XXXXXXX	≥2	XXX	XXX
XXXXXXX	≥3	XXX	XXX
	≥4	XXX	XXX
Niven et al. 2016	≥4	258	6.24
Sweeney et al. 2016	≥2**	349	4* unscheduled visits + 4* rescue OCS
Gibeon et al. 2015	≥1 Pre-optimisation:	346	4* unscheduled visits in primary care or ER + 2* hospitalisations + 6* rescue OCS
	≥1Post-optimisation:	346	1* unscheduled visits in primary care or ER + 2* hospitalisations + 3* rescue OCS

* Median number of exacerbations

** Not reported, but interquartile range was both unscheduled visits and rescue OCS use was 2-6.

Company response (4)

Administration costs

- Three hospital day cases are assumed for the first 3 visits (updated base case assumes day case admission costs of £316) to account for cannula insertion (£28.50) and increased initial monitoring time (£79.62) with a total administration cost of £108.12.
- Specialist nursing time is increased to 65 minutes from visit 4 onwards resulting in a cost of £63.88 – this accounts for the increased preparation time from 10 minutes to 20 minutes.

25-mg and 100-mg vial presentations

- No changes made to updated base case analysis with regards to drug wastage. Analysis based on the 100-mg and 25-mg vials assumes that there is no vial sharing with associated wastage
- Base case includes 25 ml vial with supporting documents provided for likely favourable approval of 25 mg vial presentation by EMA. The 25-mg vial of reslizumab is expected to be available only 3 months after the anticipated date of issue of the final NICE guidance (April 2017)
- Scenario analysis on 100 mg vial provided

Company response (5)

Other changes to base case

- No change to updated base case and response evaluated at 16 weeks (as in original analysis) based on algorithm that predicts non-response at 52 weeks. Scenario analysis conducted based on assessment of response at 6 months which demonstrated the impact on the ICER is minimal.
- The model was not updated to assess the steroid-sparing effect of reslizumab due to lack robust data.
- The base case was updated to include revised utility values estimated for exacerbation health states by the ERG. Scenario 3 proposed by ERG was followed and a weighted average was applied to estimate utility associated with the severe exacerbation health state.
- Costs associated with each health states were revised on ERG suggestion (table 98, page 169 of ERG report)

Company updated base case ≥3 exacerbations in previous year, (25 mg vial)

	Total costs		Total QALYs		
Scenario	**Reslizumab**	**BSC**	**Reslizumab**	**BSC**	**ICER**
Original base case	XXXXXX	XXXXXX	XXXXXX	XXXXXX	**£24,907**
Updated transition probabilities, no adjustment	XXXXXX	XXXXXX	XXXXXX	XXXXXX	£36,226
Adjustment to exacerbation rate observed in clinical practice in the UK	XXXXXX	XXXXXX	XXXXXX	XXXXXX	£24,008
Updated administration time	XXXXXX	XXXXXX	XXXXXX	XXXXXX	£25,642
Updated cost per health state as per ERG report	XXXXXX	XXXXXX	XXXXXX	XXXXXX	£22,278
Updated utilities: scenario 3 of ERG report	XXXXXX	XXXXXX	XXXXXX	XXXXXX	£29,732
Combined effects of all amendments (new base case)	XXXXXX	XXXXXX	XXXXXX	XXXXXX	**£25,408**
Combined effects of all amendments except for no adjustment to real world rate of exacerbations	XXXXXX	XXXXXX	XXXXXX	XXXXXX	**£43,064**

Additional scenario analysis – subgroup with ≥4 exacerbations (25mg vial)

	Total costs		Total QALYs		
Scenario	Reslizumab	BSC	Reslizumab	BSC	ICER
Base-case: ≥ 3 exacerbations in previous year	XXXXXX	XXXXXX	XXXXXX	XXXXXX	£25,408
Subgroup of patients with ≥ 4 exacerbations in previous year	XXXXXX	XXXXXX	XXXXXX	XXXXXX	£19,457
Subgroup of patients with ≥ 4 exacerbations in previous year, no adjustment to real world evidence	XXXXXX	XXXXXX	XXXXXX	XXXXXX	£40,715

BSC: Best Standard of Care; ICER: Incremental Cost-Effectiveness Ratio; mg: milligram; QALY: Quality Adjusted Life Year

Scenario analysis – assessment of response at 6 months

- Three scenarios tested to assess the impact of assessing response at 6 months according to three different definitions of response:
  - Scenario 1: no clinical asthma exacerbation over the first 6 months of treatment
  - Scenario 2 : no clinical asthma exacerbation over the first 6 months of treatment and improvement in at least one of the following clinical parameters: FEV1, ACQ or AQLQ

	Total costs		Total QALYs		
Scenario	Reslizumab	BSC	Reslizumab	BSC	ICER
Base-case	XXXXXX	XXXXXX	XXXXXX	XXXXXX	£25,408
Response assessed at 6 months - scenario 1	XXXXXX	XXXXXX	XXXXXX	XXXXXX	£24,384
Response assessed at 6 months - scenario 2	XXXXXX	XXXXXX	XXXXXX	XXXXXX	£24,384

Scenario Analysis – 100 mg vials

	Total costs		Total QALYs		
Scenario	**Reslizumab**	**BSC**	**Reslizumab**	**BSC**	**ICER**
Base-case: 25 mg vials	XXXXXX	XXXXXX	XXXXXX	XXXXXX	£25,408
Subgroup of patients with ≥ 3 exacerbations in previous year: 100 mg vials	XXXXXX	XXXXXX	XXXXXX	XXXXXX	£34,187
Subgroup of patients with ≥ 4 exacerbations in previous year: 100 mg vials	XXXXXX	XXXXXX	XXXXXX	XXXXXX	£26,525

ERG response (1)

Efficacy in target population

- Population characteristics appear to be similar in the pooled reslizumab and placebo arms.
- New 52 week efficacy results pooled from pivotal trials suggest that reslizumab compared to placebo resulted in statistically significant improvements in the exacerbation rate, severe exacerbation rate, lung function, asthma control and HRQoL in subgroups of patients who had ≥3 exacerbations in the previous year (n=158) or ≥4 exacerbations in the previous year (n=94) . Limitations include post-hoc nature of analysis and use of unexplained adjustments and sample sizes for the reslizumab and placebo arms within the exacerbation subgroups. Also, as data are confidential, ERG was unable to verify.
- Limitations also highlighted for new efficacy results for subgroup of patients optimised on treatment with high-dose inhaled corticosteroid (ICS) plus another medicinal product.

ERG response (2)

Transition probabilities

- Company states pooled subgroup of patients with ≥4 exacerbations (n=94) was 'insufficient' to estimate transition probabilities in this subgroup. However, no explanation for judgement provided.
- Transition matrix for the subpopulation with ≥4 exacerbations obtained by an adjustment based on 'real world' exacerbation rates by changing the exacerbation factor.

Rate of exacerbation in the best supportive care arm

- New " real world data" on rate of exacerbations in a severe asthma population provided on rationale that baseline exacerbation rates in the clinical trials underestimate those in clinical practice (committee had noted that the lower rates of exacerbations in the trials could reflect the effect of optimised asthma care and/or regression to the mean).
- Exacerbation rate data taken from a single cohort (Portsmouth) within the Wessex Severe Asthma Cohort (WSAC) and compared with four additional studies. However, uncertainty in the data reported as data confidential and no review methods or selection criteria reported by company

ERG response (3)

Drug wastage and evaluation of response

- The company did not amend their base case to include the 100 mg vial and evaluation of response at 6 months as requested by committee. Instead, supporting documents to support 25mg vials and response at 16 weeks was provided and requested analysis provided as scenario analyses.

Oral corticosteroid usage

- Company summarised an analysis of pooled data from the pivotal trials on OCS usage which ERG noted excluded maintenance OCS therapy and had several limitations.
- ERG further notes that published evidence is available on the oral corticosteroid-sparing effects in eosinophilic asthma of the closely-related drug mepolizumab (Bel et al.) which company did not reference

Utilities and health state costs

- The ERG agreed that updated utilities values in base case included more appropriate value for the severe exacerbation health state and the use of updated health state costs on ERG suggestion was appropriate.

Additional ERG analyses

- Exacerbation rate has a large impact on the cost-effectiveness results.
- Choice of 'real-world' data for exacerbation rate produces results that are similar to those presented in the original submission where the company increased the exacerbation rate to a rate similar to that seen in the year before treatment started.
- ERG presented a scenario where the exacerbation rate varies over time. Initially, patients have an exacerbation rate as seen in the clinical trials (reflecting better initial asthma management), i.e. with no adjustment to the rate. Over 10 years the exacerbation rate linearly increases to the exacerbation rate of the 'real world' data.

	Total costs		Total QALYs		
Scenario	Reslizumab	BSC	Reslizumab	BSC	ICER
Base-case: ≥ 3 exacerbations in the previous year; increasing BSC exacerbation rate; 25 mg	xxxxxx	xxxxxx	xxxxxx	xxxxxx	£26,952
Base-case: ≥ 3 exacerbations in the previous year; increasing BSC exacerbation rate; 100 mg	xxxxxx	xxxxxx	xxxxxx	xxxxxx	£35,471
Base-case: ≥ 4 exacerbations in the previous year; increasing BSC exacerbation rate; 25 mg	xxxxxx	xxxxxx	xxxxxx	xxxxxx	£21,439
Base-case: ≥ 4 exacerbations in the previous year; increasing BSC exacerbation rate; 100 mg	xxxxxx	xxxxxx	xxxxxx	xxxxxx	£28,754

Issues for committee

- Is ≥400/μL blood eosinophil count (as in the trials) a recognised criterion for the diagnosis of eosinophilic asthma in the UK?
- How generalisable is the trial considering the small proportion of patients in the trial that were taking oral corticosteroids at baseline? (12%-19%)
- Is the committee satisfied that a steroid sparing effect has been captured in the evidence?
- Is the committee minded to accept that clinical need is higher in patients with ≥4 exacerbations in the preceding year compared to patients with ≥3 exacerbations in the preceding year?
- Is the committee prepared to accept the "real world data" adjustment to the BSC arm in the trial which has now been suggested by the company as best representing the expected exacerbation rate in clinical practice?
- Is the committee minded to accept the company's cost-effectiveness analysis based on the 25 mg vial (instead of the 100 mg vial as requested)