NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

NICE National Institute for Health and Care Excellence

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.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Reslizumab for treating eosinophilic asthma inadequately controlled by inhaled corticosteroids

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using reslizumab in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.

- After considering these comments, the committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using reslizumab in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: **5pm, Tuesday 6 December 2016**

Second appraisal committee meeting: **Wednesday 11 January 2017**

- Details of membership of the appraisal committee are given in section 6.

1 Recommendations

1.1 The committee is minded not to recommend reslizumab within its marketing authorisation, that is, as an add-on to standard therapy for treating severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment in adults.

1.2 The committee recommends that NICE requests further clarification and an updated cost effectiveness analysis from the company, which should be made available for the second appraisal committee meeting and include:

- 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. Any adjustment related to specific subgroups should be fully explained and justified
- appropriate administration costs, including the need to go to hospital for cannula insertion and supervised infusion
- 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.
- the committee recommends that the company also considers how reslizumab may affect oral corticosteroid usage and its consequent adverse effects and their costs.

2 The technology

Description of the technology	Reslizumab (Cinqaero, Teva) is an interleukin-5 inhibitor that reduces eosinophil numbers and activity.
Marketing authorisation	Reslizumab has a marketing authorisation in the UK 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'.
Adverse reactions	The most common adverse reaction is increased blood creatine phosphokinase, which is transient and asymptomatic. For full details of adverse reactions and contraindications, see the summary of product characteristics.
Recommended dose and schedule	Intravenous infusion of 3 mg/kg body weight once every 4 weeks.
Price	The anticipated list price provided in the company submission is £499.99 per 100-mg vial (excluding VAT). The company has agreed a patient access scheme with the Department of Health. If reslizumab had been recommended, this scheme would have provided a simple discount to the list price of reslizumab with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

3 Evidence

The appraisal committee (section 6) considered evidence submitted by Teva and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of reslizumab, having considered evidence on the nature of severe eosinophilic asthma inadequately controlled by inhaled corticosteroids and the value placed on the benefits of reslizumab by

people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Patient experience

4.1 The committee understood that inadequately controlled severe eosinophilic asthma is a distressing and socially isolating condition. It heard from the patient expert that severe asthma has an unpredictable course. People with very severe asthma are often unable to work and may need help with day-to-day activities because of the symptoms. Exacerbations are very frightening and can happen without warning. They can result in frequent hospital visits and in severe cases are life-threatening, needing intubation. The committee heard from the clinical experts that standard treatment for inadequately controlled severe eosinophilic asthma is corticosteroids. These are often effective, and oral or injected corticosteroids are the mainstay of treatment for exacerbations, but when taken frequently or long term they are associated with some major complications. The patient expert explained that these include diabetes, glaucoma, weight gain, bone density loss, hip replacement, raised blood pressure and mood swings. These can have a significant impact on patients, and can mean that numerous additional medications are needed to counteract the effects of the corticosteroids. The committee heard from the patient expert that she has to attend appointments for these complications, and it takes between 2 to 4 hours daily to administer all of her medicines. The committee understood that people would welcome treatment options that replace the need for, or reduce the dose of, oral corticosteroids. The committee heard that treatments such as reslizumab reduce the number of exacerbations, and are also anticipated to reduce oral corticosteroid use. It concluded that inadequately controlled severe eosinophilic asthma is associated with substantial morbidity and that there is a need for alternative treatment options.

Current clinical management of asthma

4.2 The committee heard from the clinical experts that treatment for asthma in clinical practice follows guidelines from the British Thoracic Society and the Scottish Intercollegiate Guidelines Network (see www.brit-thoracic.org.uk). The clinical experts explained that the management of severe eosinophilic asthma lies within what were previously known as step 4 and step 5 of the superseded 2014 version of these guidelines. The current guidelines (2016) indicate that people having high-dose therapies (previously step 4) or continuous or frequent use of oral steroids (previously step 5) should be referred for specialist care. The clinical experts explained that the management of severe eosinophilic asthma lies within the high-dose therapies (previously step 4) or continuous or frequent use of oral steroids (previously step 5) stages of these guidelines. Additional therapies may include leukotriene receptor antagonists, theophyllines, oral corticosteroids, and help with smoking cessation. The committee understood that oral or injected corticosteroids can be used for short periods, for example to manage an exacerbation, but oral corticosteroids can be used as long-term maintenance. The committee was aware that the marketing authorisation for reslizumab is for 'severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment'. It questioned whether only people who continue to have exacerbations despite treatment with continuous or frequent use of oral steroids (previously step 5 of the guidelines) would be eligible for reslizumab. The clinical experts explained that people who have severe uncontrolled eosinophilic asthma having high-dose therapies (previously step 4) or continuous and frequent use of oral steroids (previously step 5) would be treated at specialist centres, and that many of these patients have asthma that will respond to optimised treatment. Reslizumab would only be considered for patients who continue to have clinically significant exacerbations despite optimised conventional treatment, and

approximately 50% of these people might be taking maintenance oral corticosteroids. The committee understood that people with severe eosinophilic asthma on optimised treatment described in the high-dose therapies (previously step 4) or continuous and frequent use of oral steroids (previously step 5) stages of the guidelines would be considered eligible for treatment with reslizumab.

Diagnosing severe eosinophilic asthma

4.3 The committee heard from the clinical experts that there are no standard diagnostic criteria for severe eosinophilic asthma in clinical practice. It heard that clinicians use the patient's phenotype to come to a probable diagnosis, which is confirmed using objective criteria in the form of evidence of eosinophilia (including blood or sputum eosinophil counts, exhaled nitric oxide levels, or biopsy specimens from nasal polyps). A rapid response to oral corticosteroids is also used to diagnose eosinophilic asthma. The committee heard that peripheral blood eosinophil count is a commonly used biomarker but it is suppressed by corticosteroid use, therefore only measurements taken before corticosteroid treatment are reliable. The clinical experts stated that measuring sputum eosinophilia gives the most accurate diagnosis of eosinophilic asthma, but this is not widely used in clinical practice. The committee acknowledged the complexity of diagnosing eosinophilic asthma.

Clinical effectiveness

Population

4.4 The committee discussed the generalisability of the clinical trials to UK clinical practice. The company presented evidence from trials that included people aged 12 to 75 years with asthma and a blood eosinophil count of 400 cells/microlitre or more, inadequately controlled with medium to high-dose inhaled corticosteroids. The committee noted that the key

trials, study 3082 and study 3083, included people with a blood eosinophil count of more than 400 cells/microlitre in the previous 12 months. The committee was aware that the marketing authorisation for reslizumab does not specify a specific eosinophil count because the European Medicines Agency stated that blood eosinophil levels are not sufficiently predictive to include a cut-off value. The clinical experts stated that the high eosinophil count threshold was a limitation of the clinical trials because reslizumab is more effective the higher the eosinophil count, and therefore it might not be as effective in clinical practice as in the trials. They also explained that some patients in the trials may have had sensitivity to fungal allergens, which would account for the high eosinophil counts observed at baseline. However, the clinical experts clarified that people with lower eosinophil counts than those in the trials may also potentially benefit from treatment with reslizumab. The committee noted that a small proportion of patients in the trials were taking oral corticosteroids, but they were not permitted to reduce their corticosteroid dose during the trial. The committee concluded that the studies are relevant to the UK but that, 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.

Frequency of exacerbations

4.5 The committee noted that study 3082 and study 3083 recruited people with 1 or more exacerbations in the previous year. It was aware that the company proposed, and presented a base case cost-effectiveness analysis for, a restricted population including people with 3 or more exacerbations per year. The committee heard from the clinical experts that they would particularly like to have this treatment available for patients having maintenance oral corticosteroids who have 3 or more exacerbations per year. However, the committee also heard that the number of exacerbations in one year is not necessarily indicative of future

exacerbation rates, and that event rates vary in patients from year to year. It considered that this is a limitation of the trials, which looked at only one year in what is a variable and lifelong condition. The committee concluded that a criterion based on the number of exacerbations was not unreasonable, and expressed the view that the more frequent the exacerbations, the greater the clinical need.

4.6 The committee discussed whether treatment with reslizumab would be appropriate for people who do not take maintenance oral corticosteroids. The clinical experts highlighted that probably at least 50% of patients on what were previously known as steps 4 or 5 of the British Thoracic Society and Scottish Intercollegiate Guidelines Network guidelines (see www.brit-thoracic.org.uk) are being treated with maintenance oral corticosteroids, but still have several exacerbations. The clinical experts explained that these people would be eligible for treatment with reslizumab but there are also other patients, who are not taking maintenance oral corticosteroids, who would benefit from reslizumab treatment. Patients who are not being treated with maintenance oral corticosteroids may receive one of the following maintenance treatments in addition to high-dose inhaled corticosteroids: leukotriene receptor antagonists, theophylline, slow-release beta-2 agonists or tiotropium. The committee considered the clinical experts' statements that maintenance corticosteroids are an effective treatment for people with severe asthma, and that a proportion of people who are taking maintenance corticosteroids will still have uncontrolled severe eosinophilic asthma. The committee noted that there are limited data on the effectiveness of reslizumab in people who are on maintenance corticosteroids, because only 19% and 12% of people respectively in study 3082 and study 3083 fulfilled this criterion. However the committee concluded that treatment with reslizumab may be considered for people who are not taking maintenance oral corticosteroids but that it would be most beneficial for people who have multiple exacerbations despite maintenance oral corticosteroid use.

Direct comparison with best supportive care

4.7 The committee considered the results from the trials, including study 3082 and study 3083. It noted that reslizumab, compared with placebo, was associated with lower rates of clinically significant exacerbations. The committee concluded that, compared with placebo, reslizumab is effective in reducing the rate of clinically significant exacerbations.

Indirect treatment comparison with omalizumab

4.8 The committee noted that the NICE scope included omalizumab as a comparator in a small 'overlap' population of people who also had severe persistent allergic IgE-mediated asthma, and therefore could have either reslizumab or omalizumab. It heard that clinicians would decide which drug is most appropriate based on the person's phenotype. For predominantly eosinophilic symptoms, such as nasal polyps and sinusitis, people would be offered reslizumab. People with predominantly IgE related symptoms, such as eczema and urticaria, would be offered omalizumab. The committee noted that the company had presented an indirect treatment comparison using data from study 3082 and study 3083 for reslizumab and from the INNOVATE and EXTRA trials for omalizumab. It noted that the company based its comparison on the full trial populations, but there are fundamental differences between them. The committee acknowledged that the 2 drugs have different mechanisms of action and different populations. It also considered that adjusting for these differences in the very small overlap population was unlikely to be robust. The committee concluded that the results from the company's indirect comparison of reslizumab with omalizumab were highly uncertain and not suitable for decision-making. The committee therefore did not consider this comparison further.

Cost effectiveness

4.9 The committee considered the company's cost-effectiveness analysis. It noted that the company's base case was for reslizumab compared with standard care, for people with severe asthma who have had 3 or more exacerbations in the previous year. The committee noted that this is a subgroup of the overall trial population of people with severe asthma who have had 1 or more exacerbations in the previous year. The committee recalled its previous conclusion (see section 4.4) that neither the trials, nor the base-case populations, accurately reflect patients in the UK who might be considered for reslizumab; people with severe disease despite optimised care, often with lower eosinophil counts than in the trials, and with higher rates of maintenance corticosteroid use. The committee noted that the company had also presented cost-effectiveness analyses comparing reslizumab with omalizumab. The committee recalled its previous conclusion (see section 4.8) that the comparison with omalizumab is highly uncertain and not suitable for decision-making. The committee concluded that it would only consider the company's analysis for reslizumab compared with best standard care using the results from study 3082 and study 3083.

4.10 The committee discussed the choice of standard care in the company's model. The committee was aware that the model did not incorporate stopping or reducing the dose of oral corticosteroids, because oral corticosteroid dose had been kept constant in the trials. It queried whether standard care with long-term maintenance oral corticosteroids is a more appropriate comparator than standard care with oral corticosteroids taken in short courses. The committee recalled the evidence from the clinical experts that 50% of patients with severe eosinophilic asthma may already be on maintenance oral corticosteroids. The clinical and patient experts stated that the long-term effects of oral corticosteroid treatment are serious and could become as problematic as the asthma itself (see

section 4.9). The clinical experts stated some observational data exist on oral corticosteroid sparing and the costs associated with treatment of corticosteroid-induced complications. The committee concluded that because more patients in UK clinical practice have maintenance oral corticosteroids than those in the trials, this is a potential benefit of reslizumab. It concluded that 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.

Exacerbation transition probabilities

4.11 The committee considered the company's approach to estimating transition probabilities between exacerbation states of the economic model. The company had noted that patients randomised to placebo, as well as those in the reslizumab arm of the trials, experienced a reduction in exacerbations. The company stated that this reflects a potential placebo effect. To account for this placebo effect, the company applied a multiplier to the exacerbation transition probabilities; the value of the multiplier was chosen so that the modelled rate of exacerbations during the first year of treatment matched the mean rate of exacerbations in the year before randomisation to the trial, in those subsequently randomised to placebo. Because the company estimated transition probabilities using data from the subgroup with 2 or more exacerbations in the previous year, the multiplier served a further purpose of adjusting the baseline rate of exacerbations to reflect the subgroup with 3 or more exacerbations, used in the base case. The company adjusted the estimates in both the placebo and the reslizumab arms. The ERG stated that it was unclear why the reslizumab arm should also be corrected for a placebo effect and the company did not provide an adequate explanation. The committee questioned how reasonable it was to make this adjustment (using a multiplier that was estimated with considerable uncertainty), because it could perhaps be accounted for by regression to the mean (that is, the

phenomenon that if patients are recruited into clinical trials when they are experiencing severe symptoms at their first assessment, they will tend to improve on their second assessment regardless of the treatment received). It also heard from the clinical experts that patients in both arms of the trials would be carefully followed and monitored during the trial, so would have had optimised, closely supervised care, which they may not have had before entering the trial. This could account for at least some of the improvement, rather than it being a placebo effect. The committee agreed that improvement could reflect the benefit of optimised care, or regression to the mean. This would be likely to affect both arms, and the adjusted rates were no more likely than the unadjusted rates to reflect the true treatment benefit of reslizumab. The committee decided that the company should have used estimates of transition probabilities directly from the relevant subgroup of the trials (3 or more exacerbations in the base case), without any adjustment for a placebo effect in either arm of the economic model. The combined adjustment for baseline exacerbation frequency and placebo effect meant that the ERG could not determine the most plausible ICER for the base-case population of 3 or more exacerbations. The committee concluded that it would have preferred to see results from a model that used the observed (unadjusted) data from the relevant subgroup in the trials to determine the transition probabilities. If there are insufficient data to estimate transition probabilities in a particular subgroup then use of 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.

Duration of treatment

4.12 The committee discussed the duration of treatment with reslizumab assumed by the company in its model. The committee noted the company's algorithm that calculated the expected response at the end of the year based on an early response at 16 weeks. The clinical experts

stated that patients would not routinely be assessed for response to reslizumab at 16 weeks because this is too early to assess the effect on exacerbations, and other measures would not be reliable enough. A more appropriate reassessment period would be 6 months, followed by annual reassessments. The clinical experts stated that if patients continued to benefit from treatment, they would remain on reslizumab indefinitely. The committee concluded that the economic modelling should include reassessment of patients at time points relevant to UK clinical practice.

Administration costs and drug wastage

4.13 The committee considered the administration costs used by the company in its model. The company assumed that administering reslizumab takes 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). The ERG indicated that treatment would initially be done as a day-case admission but monitoring time would decrease as responsiveness and safety were established for the patient. The clinical experts stated that the administration costs might be considerably higher because a day-case admission for intravenous infusion is associated with significant costs, particularly when compared with treatments like omalizumab that are given subcutaneously. The committee concluded that the company should have included more appropriate administration costs for reslizumab in its model.

4.14 The committee noted that reslizumab has a marketing authorisation at a dose of 3 mg/kg given intravenously every 4 weeks, using a 100-mg vial. The committee was aware that the company presented clinical-effectiveness evidence for the licensed 100-mg vial, but that it had applied for a licence extension to include a 25-mg vial. The company had assumed availability of the 25-mg vial in its economic model. The committee was aware that the licence extension is not expected until mid-2017 and it is not guaranteed to receive regulatory approval. The

committee concluded that vial wastage in the economic modelling should be based on the licensed 100-mg vial of reslizumab, including sensitivity analyses around the sharing of vials.

Utility values

4.15 The committee discussed the estimates of utility in the model. It noted that the company's base case used published utility values from Willson et al. (2014) and Lloyd et al. (2007) rather than mapping Asthma Quality of Life Questionnaire (AQLQ) values collected in the trials to EQ-5D. The committee noted the company's justification for using these published values, that they were used in previous NICE appraisals and are direct EQ-5D values. The ERG's view was that the company's base case should have used values mapped from AQLQ to EQ-5D, because the evidence came from the trials. The company presented a scenario analysis incorporating the AQLQ values mapped to EQ-5D. Although the ERG requested full details of the AQLQ and mapped EQ-5D utilities, none were provided by the company. As a result, the ERG could not validate those results. The committee concluded that it would have preferred the company to supply and explain the utility values calculated from the trials.

4.16 The company presented its base case taking into account the patient access scheme discount applied to reslizumab compared with best standard care. The company's base case ICER for people with 3 or more exacerbations in the previous year is £24,907 per quality-adjusted life year (QALY) gained. The committee noted that it was not presented with results for its preferred subpopulation, that is:

- not limited by blood eosinophilia count
- 3 or more, or 4 or more exacerbations in the previous year, and
- limited to patients with severe eosinophilic asthma despite receiving optimised best supportive care at an asthma specialist centre.

The committee considered that the closest population to this was in the ERG's analysis including patients with 2 or more exacerbations in the previous year, which was based on transition probabilities for exacerbations that were not adjusted to the previous year (not adjusted for placebo effect). However, these were also not adjusted to provide the transition probability for the 3 or more exacerbation subgroup, which is the population of interest in the base case. The resulting ICER is £50,878 per QALY gained. The committee was concerned that the 2 estimates, from the company and the ERG, are not related to the same population. Not adjusting for the placebo effect would be likely to increase the company base case ICER above the level that could be considered a cost effective use of NHS resources for people with 3 or more exacerbations. However, the committee concluded that the company should have an opportunity to submit a further cost-effectiveness analysis, taking into account the committee concerns, with no adjustment for placebo effect but including an analysis of the cost effectiveness for people with 3 or more, or 4 or more exacerbations in the previous year, assuming that they are treated in specialist centres with fully optimised care.

4.17 The committee was not satisfied that the cost-effectiveness analysis presented by the company accurately reflected the clinical effectiveness of this treatment in the relevant patient group in the NHS, or the relevant costs. The committee recommends that NICE requests further clarification and an updated cost effectiveness analysis from the company, which should be made available for the second appraisal committee meeting and include:

- 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 be adjusted to take account of a placebo effect. Any adjustment related to specific subgroups should be fully explained and justified

- appropriate administration costs including the need to go to hospital for cannula insertion and supervised infusion
- drug wastage using only the licenced100-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
- the committee recommends that the company also considers how reslizumab may affect oral corticosteroid usage and its consequent adverse effects and their costs.

4.18 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view in this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

4.19 The committee heard from stakeholders that reslizumab is innovative in its potential to make a significant and substantial impact on health-related benefits. The committee heard from the clinical experts that there are few treatments for severe eosinophilic asthma that have the potential to reduce corticosteroid use. It noted that it had not seen any evidence on preventing or delaying maintenance oral corticosteroids but heard from the clinicians that this is an important aim of treatment with reslizumab. The committee discussed the analysis presented by the company to

capture the benefits of reducing oral corticosteroid use, separate to any benefits from reducing exacerbations. The committee noted that the impact on the ICERs was negligible and heard from the ERG and the company that there were limitations in the analysis. The committee agreed that some benefits related to avoiding the significant adverse effects of oral corticosteroid use had not been fully captured in the QALY measure. The committee also considered that there were benefits to carers, which may not have been captured in the QALY calculation. The committee therefore agreed that reslizumab could be considered innovative.

Summary of appraisal committee's key conclusions

TAXXX	**Appraisal title: Reslizumab for treating severe eosinophilic asthma inadequately controlled by inhaled corticosteroids**	**Section**
Key conclusion		
The committee is minded not to recommend reslizumab within its marketing authorisation, that is, as an add-on to standard therapy for treating severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal drug product for maintenance treatment in adults. The committee recommends that NICE requests further clarification and an updated cost effectiveness analysis from the company, which should be made available for the second appraisal committee meeting and include: • 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. Any adjustment related to specific subgroups should be fully explained and justified		1.1, 1.2

• appropriate administration costs, including the need to go to hospital for cannula insertion and supervised infusion • 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 • the committee recommends that the company also considers how reslizumab may affect oral corticosteroid usage and its consequent adverse effects and their costs.		
Current practice		
Clinical need of patients, including the availability of alternative treatments	The committee understood that people with severe eosinophilic asthma on optimised treatment, described in the high-dose therapies (previously step 4) or continuous and frequent use of oral steroids (previously step 5) stages of the guidelines from the British Thoracic Society and the Scottish Intercollegiate Guidelines Network, would be considered eligible for treatment with reslizumab.	4.2

Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The committee concluded that, compared with placebo, reslizumab is effective in reducing the rate of clinically significant exacerbations.	4.7
What is the position of the treatment in the pathway of care for the condition?	The committee concluded that treatment with reslizumab may be considered for people who are not taking maintenance oral corticosteroids but that it would be most beneficial for people who have multiple exacerbations despite maintenance oral corticosteroid use.	4.6
Adverse reactions	The most common adverse reaction is increased blood creatine phosphokinase, which is transient and asymptomatic.	Section 2
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The committee noted that there is limited data on the effectiveness of reslizumab in people who are on maintenance corticosteroids, because only 19% and 12% of people respectively in study 3082 and study 3083 fulfilled this criterion. However, the committee concluded that treatment with reslizumab may be considered for people who are not taking	4.6

	maintenance oral corticosteroids but that it would be most beneficial for people who have multiple exacerbations despite maintenance oral corticosteroid use.	

Relevance to general clinical practice in the NHS	The committee concluded that the studies are relevant to the UK but that, 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.	4.4
Uncertainties generated by the evidence	The committee noted that study 3082 and study 3083 recruited people with 1 or more exacerbations in the previous year, but the clinical experts stated that they would particularly like to have this treatment available for patients having maintenance oral corticosteroids who have 3 or more exacerbations per year. The committee concluded that the results from the company's indirect comparison of reslizumab with omalizumab were highly uncertain and not suitable for decision-making. The committee therefore did not consider this comparison further.	4.5, 4.8
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The committee concluded that patients with more exacerbations have a greater clinical need.	4.5

Estimate of the size of the clinical effectiveness including strength of supporting evidence	The committee concluded that, compared with placebo, reslizumab is effective in reducing the rate of clinically significant exacerbations.	4.7
Evidence for cost effectiveness		
Availability and nature of evidence	The committee noted that the company had presented cost-effectiveness analyses comparing reslizumab with omalizumab but that the comparison with omalizumab is highly uncertain and not suitable for decision-making. The committee concluded that it would only consider the company's analysis for reslizumab compared with best standard care using the results from study 3082 and study 3083.	4.9

Uncertainties around and plausibility of assumptions and inputs in the economic model	The committee noted that the company's combined adjustment for baseline exacerbation frequency and placebo effect meant that the ERG could not determine the most plausible ICER for the base-case population of 3 or more exacerbations.	4.11

Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The committee noted that the company's base case used published utility values from Willson et al. (2014) and Lloyd et al. (2007) rather than mapping Asthma Quality of Life Questionnaire (AQLQ) values collected in the trials to EQ-5D, and concluded that it would have preferred the company to supply and explain the utility values calculated from the trials. The committee was aware that the model did not incorporate stopping or reducing the dose of oral corticosteroids, because oral corticosteroid dose had been kept constant in the trials. The committee concluded that because more patients in UK clinical practice have maintenance oral corticosteroids than those in the trials, it would be reasonable for the company to consider how reslizumab may affect oral corticosteroid usage and its consequent adverse effects and their costs.	4.15, 4.10

Are there specific groups of people for whom the technology is particularly cost effective?	The committee noted that it was not presented with results for its preferred subpopulation, that is: • not limited by blood eosinophilia count • 3 or more, or 4 or more exacerbations in the previous year, and • limited to patients with severe eosinophilic asthma despite receiving optimised best supportive care at an asthma specialist centre. The committee concluded that it would have preferred to see results from a model which used the observed (unadjusted) data from the relevant subgroup in the trials to determine the transition probabilities.	4.16, 4.11
What are the key drivers of cost effectiveness?	The calculation and choice of exacerbation transition probabilities was the key driver of cost effectiveness for reslizumab compared with best supportive care.	4.11

Most likely cost-effectiveness estimate (given as an ICER)	The committee considered that the closest population to its preferred subpopulation was in the ERG's analysis that included patients with 2 or more exacerbations in the previous year, which was based on transition probabilities for exacerbations that were not adjusted to the previous year (not adjusted for placebo effect). The resulting ICER was £50,878 per QALY gained. However, the transition probabilities were also not adjusted to provide the transition probability for the 3 or more exacerbation subgroup, which is the population of interest in the base case.	4.16
Additional factors taken into account		
Patient access schemes (PPRS)	A patient access scheme discount was applied to the ICERs presented by the company and the ERG for reslizumab compared with best standard care.	4.16
End-of-life considerations	Not applicable	
Equalities considerations and social value judgements	No equalities issues were identified.	

5 Proposed date for review of guidance

5.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Dr Jane Adam
Chair, appraisal committee
October 2016

6 Appraisal committee members, guideline representatives and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Richard Diaz

Technical Lead

Joanna Richardson

Technical Adviser

Liv Gualda

Project Manager

Response to Appraisal Consultation Document (ACD)

Reslizumab for treating eosinophilic asthma inadequately controlled by inhaled corticosteroids

ID 872

Teva UK

06 December 2016

Table of contents

1 Executive summary

Teva welcomes the opportunity to respond to the committee's conclusions in the Appraisal Consultation Document (ACD). We are disappointed by the initial decision but appreciate the opportunity to respond to the requests for additional analyses. The ACD raised a number of issues regarding the evidence base and the modelling assumptions used to support the use of reslizumab for treating eosinophilic asthma inadequately controlled by corticosteroids within the National Health Service (NHS). In particular, following the committee's recommendation, NICE requested Teva to provide further clarifications and an updated cost-effectiveness analysis that includes:

- 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. Any adjustment related to specific subgroups should be fully explained and justified.
- Appropriate **administration costs**, including the need to go to hospital for cannula insertion and supervised infusion.
- 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.

The committee recommended that the company also consider how reslizumab may affect **oral corticosteroid usage** and its consequent adverse effects and their costs.

This response aims to address these requests and provide the updated cost-effectiveness analysis. In addition, following approval from NICE, Teva is submitting new evidence about the real-world burden of exacerbations in the target population in the UK, as well as additional data on the efficacy of reslizumab in the target population. The updated base case is as follows:

- **Population & outcomes**:
    - The base case population relates to patients with 3 or more exacerbations in the previous year. The justification for this choice and new clinical trial evidence in this subgroup of patients are included in this response.
    - Exacerbation rates or more specifically transition probabilities for patients with ≥3 exacerbations have been estimated based on the subgroup of patients who had experienced 3 exacerbations or more prior to enrolment in the pivotal clinical trials (studies 3082 & 3083).

        - Probabilities were then adjusted to account for the average annual number of exacerbations reported in the real-world clinical practice in the UK despite follow-up and best standard of care at specialist asthma centres.
        - A scenario analysis has been performed without adjustment of the rate of exacerbations.
    - Full results for the population with 4 or more exacerbations in the previous year are also provided as part of a scenario analysis.

- **Administration costs**:
    - Three hospital day cases are assumed for the first three visits to account for cannula insertion and increased initial monitoring time at the first three administrations of reslizumab.
    - Nursing time is increased to 65 minutes from visit four onwards – this accounts for the increased preparation time from 10 minutes to 20 minutes.
- **Vials and dosing:** both 25-mg and 100-mg vials and corresponding wastage are included:
    - New evidence supporting the timing of licensing and availability of the 25-mg vial presentation – with European Commission (EC) decision expected in [redacted] – is provided.
    - The ICER assuming the sole use of the licensed 100-mg vial with associated wastage or vial sharing are also presented as scenario analyses.
    - A scenario analysis is provided based on the vial-based dosing (VBD) that is anticipated to be included in the Summary of Product Characteristics (SPC) in [redacted] with the marketing authorization of 25-mg vial. VBD reduces wastage, decreases costs, simplifies preparation and reduces preparation time.
- **Response to treatment:** the 16-week evaluation of response has been kept in the base case analysis as:
    - Teva has re-evaluated response at 24 weeks [redacted]
    - Clinically, it is important to get an early assessment of response for optimizing patient care. As reslizumab has shown benefit in the disease control, lung function and quality of life by 16 weeks, it is the most appropriate time for the first clinical assessment. New evidence is provided to demonstrate early effect of reslizumab in patients with 3 or more exacerbations in the previous year

- It is also the time point that is currently used for omalizumab, which has become well established in clinical practice.

- **ICER:** the individual and combined effects of all amendments are presented in this response.
- **Oral corticosteroid usage**: OCS sparing effect is not included in the updated base case; Although the committee requested additional evidence on OCS sparing, no data are available yet on the steroid sparing effect of reslizumab. This is currently under assessment in an ongoing study.
- **Other amendments to the updated base case:** Although not specifically requested by the committee, costs and utility estimates were updated according to the recommendations made from the Evidence Review Group.

As discussed at the Committee meeting, Teva is submitting new evidence on the effect of reslizumab on the frequency of exacerbations as well as lung function, disease control, quality of life and symptoms in subgroups of patients with ≥3 exacerbations in the previous year (N=158). These data are based on post-hoc analyses of the two 52-week pivotal clinical trials (studies 3082 & 3083) in adults with British Thoracic Society (BTS) step 4&5, same population that was used to estimate updated transition probabilities. It showed that reslizumab reduces the frequency of exacerbations by [redacted] We are also submitting further evidence in two other subgroups of patients with 3 or more exacerbations in the previous year: patients meeting the exact criteria within the license; patients on OCS maintenance treatment. This shows that the reslizumab relative treatment effect is consistent across all relevant patient population.

Teva is also submitting new evidence of the real-world burden of severe exacerbations in the target population based on a number of published and unpublished studies of various UK severe asthma cohorts. [redacted] This study is used in the base case to adjust the transition probabilities to account for the real-world frequency of exacerbations in the relevant patient population in the UK.

Below is a summary of the incremental cost-effectiveness ratios (ICERs) resulting from each implemented amendments. The updated health economic model results in the updated base case ICER of **£25,408** per Quality Adjusted Life Year (QALY) gained.

Summary of ICERs with the new assumptions in the updated base case.

Scenario	ICER
Initially submitted model, Patient Access Scheme (PAS) price	**£24,907**
• Patients with 3 or more exacerbations in the previous year – updated transition probabilities	£36,226
• Patients with 3 or more exacerbations in the previous year and adjustment to exacerbation rate observed in clinical practice in the UK	£24,008
• Updated administration costs • Updated cost per health state as per ERG report	£25,642 £22,278
• Updated utilities: scenario 3 of ERG report	£29,732
Combined effects of all amendments	**£25,408**

In addition to the updated base case several scenario analyses have been run in order to address alternative assumptions for the requests made by NICE – crucially:

- Assuming only the 100-mg vial is available and accounting for full associated wastage the reslizumab was associated with an ICER of £34,187/QALY. With vial sharing, the associated ICER is £23,483/QALY
- The cost-effectiveness of reslizumab in the subgroup of patients with 4 exacerbations or more in the previous year was estimated at £19,457/QALY

The committee concluded inadequately controlled severe eosinophilic asthma is associated with substantial morbidity and there is a need for alternative treatment options. Considering Teva updated assessment of cost-effectiveness, the target population likely to obtain the most benefit from the treatment, and having addressed the committee's concerns regarding evidence base and the key assumptions in the health economic model, **we would ask the committee to re-assess the clinical and cost-effectiveness of reslizumab as add-on therapy in adult patients with severe eosinophilic asthma inadequately controlled despite high dose inhaled corticosteroids and other medicinal product for maintenance treatment in adults and with 3 exacerbations or more in the previous year.**

2 Teva's Detailed Response to the Appraisal Consultation Document (ACD)

2.1 Population and transition probabilities

The Committee requested further clarification and an updated cost-effectiveness analysis on "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. Any adjustment related to specific subgroups should be fully explained and justified."(1)

2.1.1 Population

Teva considered appropriate the subgroup of patients with 3 or more exacerbations in the previous year for the updated base case analysis for the following reasons:

- This subgroup was first identified based on feedback from clinical experts, who highlighted the therapeutic need in this patient population as reported in the initial Teva submission.
- Patients with 3 or more exacerbations per year are substantially more likely to experience more exacerbations in the following year than patients with less than 3. This assessment is supported by a publication by Price *et al*, who reported the odds of experiencing 2 exacerbations or more in a given year as a function of a number of factors, including the number of exacerbations in the preceding year (based on a multivariate logistic regression analysis). The authors reported that the odds of experiencing two exacerbations or more is:
    - 25.7 times higher in patients who have experienced 3 exacerbations or more in the preceding year than in patients who have not experienced any exacerbation,
    - 6.8 times higher in patients who have experienced 3 exacerbations or more in the preceding year than in patients who have experienced only one exacerbation and
    - 3.5 times higher in patients who have experienced 3 exacerbations or more in the preceding year than in patients who have experienced two exacerbations in the preceding year.(2)
- The study did not report specific data for patients with 4 or more exacerbations per year.
- The efficacy of reslizumab in this subgroup is even greater than in the general population of adult patients in BTS step 4 or 5 (2.1.2). At the same time, there is limited difference in the relative treatment effect of reslizumab between the subgroups of patients with ≥3 or ≥4 exacerbations in the previous year.

- In addition, as reported in the ACD report, the clinical experts indicated that they "would particularly like to have reslizumab available for patients having maintenance oral corticosteroids who have 3 or more exacerbations per year" (NICE, 2016: ACD, p.22).
- As shown in the Table 1 below – which describes the baseline characteristics of the subgroup from the two pivotal clinical trials with ≥3 exacerbations in the previous year – the patient population with 3 or more exacerbations in the previous year has a very severe disease especially with respect to the level of disease control (ACQ), lung function (FEV1) and quality of life (AQLQ)
- Frequent exacerbations account for considerable burden of disease and costs, and if reslizumab is deemed effective and cost effective in this population, its availability to NHS patients would address considerable unmet need.

[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]

The detailed results for the population with 4 or more exacerbations per year are reported in scenario analysis.

2.1.2 Efficacy in the target population

Analyses of the two pivotal trials (studies 3082 & 3083) demonstrate that reslizumab is particularly effective in patients with ≥3 exacerbations in the previous year. In the population that was used to estimate transition probabilities of 158 adult patients with BTS step 4&5 with ≥3 in the previous year, reslizumab was shown over the 52-week observation period to reduce the frequency of exacerbations by [redacted]

[redacted]

[redacted]

Number of exacerbation in the previous year	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥**3**	158	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥**4**	94	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Similar effects of reslizumab were also observed in a subgroup of [redacted] patients with ≥3 and ≥4 exacerbations in the year preceding enrolment in the trial, who were optimised on treatment with high-dose ICS and another medicinal product for maintenance treatment as per reslizumab licensed population. In this patient population, the impact on exacerbation rate reduction was largely similar to a broader population reported above. At the same time, the impact on lung function, disease control, quality of life and symptom control for population of ≥3 in the preceding year were all statistically significant and above the levels of minimal clinically important difference. [redacted] This indicates that reslizumab not only benefits patients in terms of reduction of exacerbations, but also improves patients ability to breath and, with better quality of life, enables them to improve asthma control and quality of life between the periods of exacerbations.

[redacted]

Number of exacerbation in the previous year,	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

2.1.3 Transition probabilities

In the updated base case analysis in this response, the transition probabilities for reslizumab and BSC were estimated based on patients who had experienced 3 exacerbations or more in the year preceding enrolment in the two 52-week pivotal clinical trials (N=158 in both active and placebo arm combined).

- In the initial submission, the transition probabilities were generated based on broader population of patients with 2 and more exacerbations in the previous year. As already mentioned at the committee meeting, new analyses have been undertaken to generate the transition matrix specific to the target population.
- The smaller sample of patients who had experienced at least 4 exacerbations (N=94 in both active and placebo arm combined) was insufficient to estimate the transition probabilities in this subgroup. Hence, the transition matrix for this population was estimated based on the transition matrix observed in patients having experienced 3 exacerbations or more but adjusted the incidence of exacerbations to reflect the mean rate of exacerbations observed in clinical practice for this specific subgroup (see section 0).

The updated transition matrices are reported in appendix.

2.1.4 Rate of exacerbation in the BSC arm

The rate of exacerbations in the BSC arm for the cost-effectiveness analysis was estimated using real world data from a UK severe asthma registry.

- As stated in the NICE requirements for the reference case, "the estimate of the overall net treatment effect of an intervention is determined by the baseline risk of a particular condition or event and/or the relative effects of the technology compared with the relevant comparator treatment."(3) (p.53)
- Our previous approach to estimate the baseline risk of exacerbations relied on the adjustment to the rates of exacerbations in the year preceding enrolment in the clinical trials. This adjustment was deemed inappropriate by the committee.
- Instead, real world evidence on exacerbation rates in the target population treated for severe asthma in the NHS was therefore obtained. This evidence from clinical practice was used to account for baseline risk of exacerbations. In the appendix, we explain how specifically this adjustment have been made to the transition probabilities.

[redacted]

[redacted]

[redacted]

[redacted]

These exacerbation rates are strongly supported by other evidence from real world severe asthma cohorts in the UK. A targeted review was conducted to identify studies documenting the rate of exacerbation in the population of interest. The identified studies and the main findings are reported in Table 1.

Table 1. Rates of exacerbation reported for real world severe asthma cohorts in the UK.

Study	Number of severe exacerbation in the year	Sample size	Mean number of severe exacerbations
[redacted]	≥1	[redacted]	[redacted]
	≥3	[redacted]	[redacted]
	≥4	[redacted]	[redacted]
[redacted]	≥1	[redacted]	[redacted]
	≥2	[redacted]	[redacted]
	≥3	[redacted]	[redacted]
	≥4	[redacted]	[redacted]
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.

[redacted]

Niven *et al*. recently published a study which involved 258 adults with severe asthma treated at 22 NHS centres, including specialist centres and district general hospitals in the UK[1].(5) Centres participating in this study were expected to be following the national (NICE or SMC) guidelines. The mean age of patients was 44.7 years, and mean duration of asthma 25.1 years. The authors reported that patients with ≥4 exacerbations had a mean annual exacerbation rate of 6.24 (4.58 exacerbations per year were identified as leading to a 10 mg or more increase in OCS at any point for at least 3 days and 1.66 exacerbations per year were associated with ER visits or hospital admission).

[1] London, Manchester, Bradford, Glasgow, Plymouth, Leeds, Birmingham, Belfast, Southampton, Hull, Huddersfield, Merthyr Tydfil, Gateshead, Torquay, Stevenage, Middlesbrough, Chertsey, Swansea

Two studies of similar severe asthma cohorts conducted in the UK reported considerably higher rates of exacerbations. Sweeney et al. studied patients from four UK specialist centres in the British Thoracic Society Difficult Asthma Network and reported a median of 4 rescue oral corticosteroid administrations and 4 unscheduled visits per year.(6) Gibeon et al. studied a cohort of severe patients with asthma who had their treatment optimised in a specialised asthma centre.(7) The authors reported a median of 4 unscheduled primary care or ER visits, 2 hospitalisations and 6 rescue OCS courses in the year preceding optimisation. At follow-up, with additional treatments such as omalizumab (16.9% of patients), the median exacerbation rate decreased to 1 unscheduled visit, 2 hospitalisations and 3 rescue oral corticosteroid administrations. [redacted]

2.2 Administration costs

The Committee requested further clarification and an updated cost-effectiveness analysis accounting for "appropriate administration costs, including the need to go to hospital for cannula insertion and supervised infusion." Reslizumab is administered intravenously and it is expected to be administered in specialist asthma centres.(8)

In the original analysis, the cost of administration of reslizumab was based on 55 minutes specialist nurse time from first visit. In the updated base case, we have updated treatment costs as follows:

- Three hospital day cases are assumed for the first 3 visits to account for cannula insertion and increased initial monitoring time.
- Nursing time is increased to 65 minutes from visit 4 onwards – this accounts for the increased preparation time from 10 minutes to 20 minutes.

We have increased significantly the costs for the first 3 visits for the following reasons:

- A clinical expert to the ERG indicated that the treatment would initially be done as a day-case admission, but that the monitoring time would decrease as responsiveness and safety were established for the patient.
    - The updated base case assumes that day-case admissions costs (HRG code DZ15R, £316, see details in appendix) (9)
    - Based on microcosting approach, the total cost of administrations would not be higher than £108.12 including:
        - £79.62 for the total nursing time.
        - £28.50 for cannula insertion (see appendix for details)
- 2 out of 3 severe allergic reactions reported in patients treated with reslizumab in the safety dataset submitted to FDA took place after the second infusion.(10)

From the fourth administration, the following approach has been used:

- As stated in the reference case (3) (p.44) "data based on HRGs may not be appropriate in all circumstances (for example, when (…) the mean cost does not reflect resource use in relation to the new technology under appraisal). In such cases, other sources of evidence, such as micro-costing studies, may be more appropriate."
- Following suggestion to extend preparation time by a clinical expert consulted by the ERG,(11) this time has been doubled from 10 minutes to 20 minutes, resulting in the total time of 65 minutes of specialist nurse time and the cost of £63.88.

Teva anticipates that the administration costs of reslizumab will overall be further reduced and the process optimised due to the following:

- Teva will launch its Support Solutions programme designed to assist patients when reslizumab is added to their existing asthma treatment plan. The programme will assists NHS healthcare professionals in helping people with the transition to infusion therapy that has been prescribed in addition to existing asthma management therapies by aiding their understanding of and adherence to treatment. While the cost and health impact of the programme is not captured in the model, it can be expected that administration of reslizumab will be optimised.

[redacted]

2.3 25-mg and 100-mg vial presentations

NICE requested Teva to include drug wastage using only the licensed 100-mg vial in the updated base case cost-effectiveness analysis. The updated base case analysis that we submit in this response includes both 25-mg (2.5mL) and 100-mg (10mL) vials. The key reasons for this are as follows:

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

[redacted]

As in the initial submission, the distribution of weight used to estimate the number of vials necessary to treat a patients is based on adult patients in BTS steps 4 and 5 enrolled in the pivotal trials. These patients had a mean weight of 75.2 kg. The analyses based on the 100-mg and 25-mg vials assumes that there is no vial sharing with associated wastage. As a consequence, there are no changes to the updated base case.

In line with the committee's request, an analysis based on the 100-mg vials and associated wastage is also presented as scenario analysis (see section 3.2.1).(1) A scenario with vial-sharing is presented as well as indicated in ACD (page 15).

2.4 Evaluation of response

NICE requested Teva to include in the updated base case an evaluation of response to treatment at periods that reflect clinical practice (such as 6 months from the start of treatment). The analysis in the initial submission assumed that the first assessment of response to treatment is made 16 weeks following treatment initiation, based on an algorithm that predicts non response at 52 weeks (i.e. patients predicted not to respond at 52 weeks discontinue treatment). This algorithm accounts not only for the impact of reslizumab in terms of reduction of exacerbations but also for other manifestations of patient response in terms of improved lung function, disease control and quality of life. We are providing further details about the algorithm based on recently published poster. In addition, the model assumes that beyond the first year of treatment, patients continue to be assessed so that patients continuously uncontrolled or in exacerbation for a year discontinue treatment.

This approach has been kept in the updated base case analysis for the following reasons:

[redacted]

- Clinically, it is important to get an early assessment of response for optimizing patient care. As reslizumab has shown benefit in the disease control, lung function and quality of life by 16 weeks, it is the most appropriate time for the first clinical assessment. New evidence is provided to demonstrate early effect of reslizumab at 16 weeks in patients with 3 or more exacerbations in the previous year (see [redacted])
- It is also the time point that is currently used for omalizumab, which has become well established in clinical practice.

[redacted]

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

However based on the recommendations made by the committee, a scenario analysis was conducted based on an assessment of response at 6 months (see section 3.2.5) and demonstrated that the impact on the ICER is minimal.

2.5 Oral corticosteroid usage

The committee concluded that more patients in UK clinical practice have maintenance oral corticosteroids (OCS) than those in the trials. Several long term adverse effects of OCS including bone fracture, diabetes mellitus, peptic ulcer, myocardial infarction and stroke, cataract and glaucoma, weight gain, non-Hodgkin's lymphoma, adrenal insufficiency and sleep disturbance have been highlighted by the committee assessing omalizumab. In addition, the committee concluded that other adverse effects, such as obesity, hypertension, mood changes, depression, psychosis, thinning skin, delayed wound healing, reduced growth in children and increased risk of infection were additional important factors.(12) The committee concluded that it would be reasonable for the company to explore what impact reslizumab might have on OCS usage and its related adverse effects and costs.

In the two pivotal clinical trials of reslizumab, per protocol, patients with systemic corticosteroid dependent asthma at baseline were not allowed to change their baseline systemic corticosteroid dose during the study. However a post-hoc analyses of the number of prescriptions of rescue OCS and the total cumulative dose of corticosteroid revealed that (13):

- [redacted]
- [redacted]*

The steroid sparing effect of reslizumab is currently under study in a clinical trial designed to determine the ability of reslizumab to produce a corticosteroid-sparing effect in patients with OCS-dependent asthma and elevated blood eosinophils, without loss of asthma control (NCT02501629).(14)

Given the lack of robust data to assess the steroid-sparing effect of reslizumab at this point in time, this component was not included in the cost-effectiveness model.

However, irrespective of the potential effect of reslizumab on oral cortisteroid usage, patients that are receiving maintenance OCS are likely to benefit further from the addition of reslizumab as an add-on to OCS maintenance therapy. The post-hoc analysis from the pivotal clinical trials (studies 3082 and 3083) from a small subgroup of 90 adult patients with severe disease (BTS step 4&5) that were receiving OCS as a maintenance therapy showed that the patients experience [redacted] reduction in the overall exacerbation rates almost all of which (95%) were severe in nature.

2.6 Other amendments to the updated base case

2.6.1 Utilities

Teva has revised utility values estimated for exacerbation health states by the ERG in the updated base case. We have followed the scenario 3 proposed by ERG due to the fact that the utility value presented by Lloyd et al. applies only to exacerbations leading to hospitalisation.(11) A weighted average was therefore applied to estimate utility associated with the severe exacerbation health state.

Table 2. Utility estimates by health state in initial submission and updated base case

Health state	Initial submission	Updated base case
Controlled	0.920	0.920
Uncontrolled	0.728	0.728
Exacerbation	0.570	0.570
Severe exacerbation	0.330	0.510

It is highly likely that the updated base case underestimates the full utility gain associated with reslizumab. As in the initial submission, we have assumed that the duration of exacerbations did not differ in the reslizumab and BSC arms. Additional post-hoc analyses revealed, however, that the duration of clinical asthma exacerbations among patients in the placebo arm of the two pivotal trials (studies 3082 & 3083) [redacted] in the target population in this submission, in a subgroup of adult patients with BTS GINA 4&5 with 3 or more exacerbations in the previous year. In the entire combined population ii the difference in the corresponding durations was [redacted] This additional evidence suggests that utility estimates based solely on the frequency of exacerbations markedly underestimates efficacy of reslizumab. Indeed longer exacerbations might be associated with greater severity and complications and therefore lower utility. Furthermore, with the range of duration of exacerbations of [redacted] on placebo and [redacted] on reslizumab, in many patients AQLQ would not have been adequate to capture all exacerbations due to limited recall. In addition, these data highlight particular burden of exacerbations, and therefore disutility in the population with 3 or more exacerbation in the previous year.

2.6.2 Costs

Teva has revised the costs associated with each health states on the basis of the ERG suggestion (Table 98, p169 of the ERG report) in the updated base case analysis. (11)

Table 3. Cost estimates by health state in initial submission and updated base case

Health state	Initial submission	Updated base case
Controlled	£11.86	£32.66
Uncontrolled	£45.19	£107.44
Exacerbation	£70.36	£137.74
Severe exacerbation	£649.56	£897.25

2.7 Overarching questions

2.7.1 Has all the relevant evidence been taken into account?

Teva considers that the ACD does not take into account all the relevant evidence. Specifically:

- The effect of reslizumab on rates of exacerbations, duration of exacerbations, lung function, asthma control and quality of life in patients with 3 or more and 4 or more exacerbations in the previous year was not initially submitted by Teva. This evidence is presented in this submission.
- The evidence demonstrating the baseline risk of exacerbations in the clinical practice in the NHS. This evidence combining published and unpublished data are now presented in this submission.

2.7.2 Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

Teva does not consider that the provisional recommendations in the ACD constitute a suitable basis for guidance to the NHS. Teva recommends that reslizumab is to be used in a restricted population in patients with 3 or more exacerbations per year while the provisional recommendation applies to its marketing authorisation, that is, as an add-on to standard therapy for treating severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment in adults. Indeed, the Committee was minded not to recommend reslizumab for the entire licensed population, but it requested from Teva additional evidence on efficacy of reslizumab in patients with 3 or more or 4 or more exacerbations in the previous year

2.7.3 Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Teva believes that summaries of clinical and cost effectiveness of reslizumab versus BSC and omalizumab are reasonable interpretations of the evidence. The only exception are analyses where exacerbation rates in the BSC arm are deemed representative of the target population within the NHS clinical practice. Real world evidence from severe asthma registers indicates considerably higher burden of exacerbations than that in the setting of reslizumab clinical trials.

However, Teva recognizes that previously applied adjustment for placebo response does not lead to a robust estimate of the exacerbation rates in the BSC arm. With the more robust approach based on real world evidence, no adjustment for placebo effect is needed. Importantly, the relative risk of exacerbations modelled in the updated base case matches that obtained from the randomised trial data without additional adjustment.

One piece of evidence used in the cost effectiveness analysis is the available vial size: 100-mg versus 25-mg per vial, as well as variation of vial based dosing (VBD). This evidence is of regulatory, rather than clinical or cost effectiveness nature, yet drug wastage and associated cost implications depend on the formulation used. The committee acknowledged that it was aware that the license extension for 25mg vial and VBD was not expected until [redacted] and that the extension was not guaranteed to receive regulatory approval. Teva believes that accepting only the 100mg formulation for the appraisal would not be a reasonable interpretation of the regulatory evidence. Indeed, license extension granted in [redacted] would coincide with commencement of reimbursement of reslizumab if a positive final appraisal determination were to be issued [redacted] earlier in April 2017.

Also, while positive licensing decision cannot be guaranteed or predicted with absolute certainty, current status of the licensing procedure indicates that there is no single reason for the decision to be negative or delayed. In contrast, Teva has not identified a single case of NICE technology appraisal, where the recommendation were changed following a change of drug formulation of the same efficacy, safety and cost. In fact, for every NICE appraisal there is no absolute certainty that a new formulation, associated with different drug wastage, would not be licensed and introduced following the final appraisal determination. Therefore, if any uncertainly applies to the new formulation of reslizumab, it would also apply to every other drug appraised by NICE. Taking a pragmatic approach in light of the current EMA reslizumab license extension schedule, Teva believes that use of the 25mg per vial formulation for the base case is based on a more reasonable interpretation of evidence.

2.7.4 Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion, or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Teva does not believe that there are equality related issues raised in the ACD or relevant issues needing special consideration which have not been highlighted in previous submissions and consultations.

3 Results

3.1 Updated base case

3.1.1 Base-case and impact of each amendment individually

Table 4 describes the updated proposed base case. The reslizumab strategy is estimated to result in additional costs (+£83,417) and additional QALYS (+3.09) resulting in an ICER of **£25,408**, compared with £24,907 in the original analysis. The predicted rates of exacerbations [redacted]

Table 4. Base case and impact of each amendment

	Total costs			Total QALYs			ICER
Scenario	[redacted]			[redacted]			
Initially submitted model, Patient Access Scheme (PAS) price	[redacted]			[redacted]			**£24,907**
Patients with 3 or more exacerbations in the previous year – updated transition probabilities, no adjustment	[redacted]			[redacted]			£36,226
Patients with 3 or more exacerbations in the previous year and adjustment to exacerbation rate observed in clinical practice in the UK	[redacted]			[redacted]			£24,008
Updated administration time	[redacted]			[redacted]			£25,642
Updated cost per health state as per ERG report	[redacted]			[redacted]			£22,278
Updated utilities: scenario 3 of ERG report	[redacted]			[redacted]			£29,732
Combined effects of all amendments	[redacted]			[redacted]			**£25,408**

BSC: Best Standard of Care; ICER: Incremental Cost-Effectiveness Ratio; PAS: Patient Access Scheme; QALYs: Quality-Adjusted Life Years

3.1.2 Deterministic sensitivity analysis

Results of the deterministic sensitivity analysis are presented in Figure 1 and Table 5.

[redacted]

Figure 1. Tornado diagram - deterministic sensitivity analysis

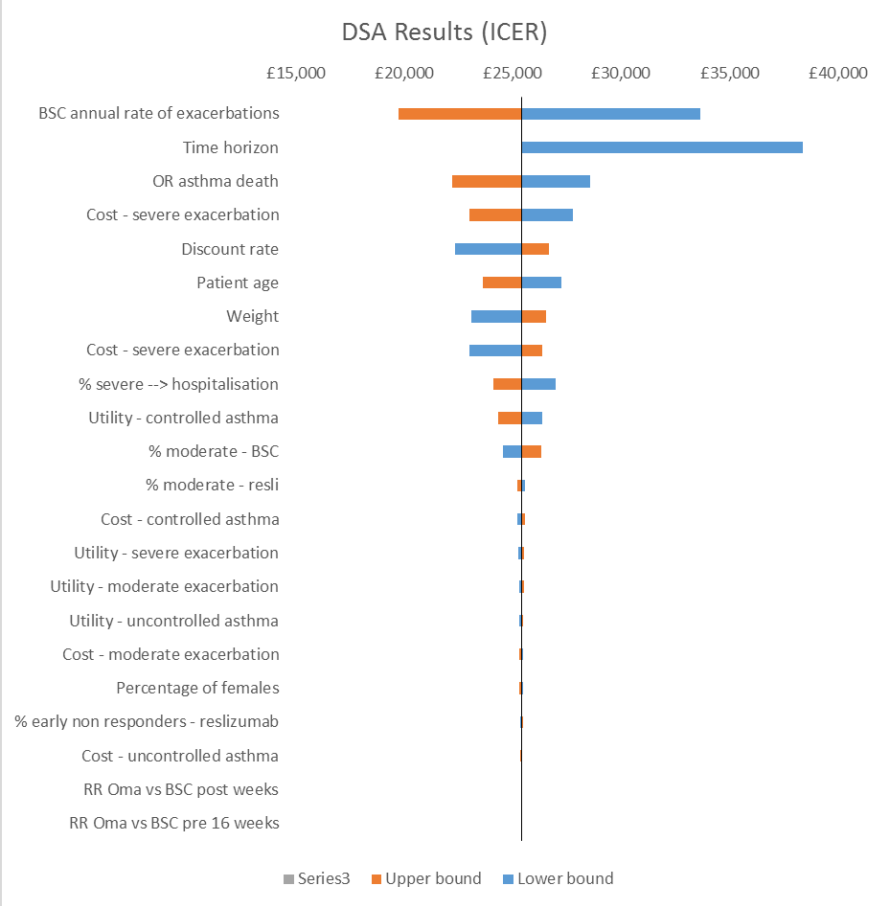


Table 5. Deterministic sensitivity analysis: detailed results

Parameter	ICER Lower bound	ICER Upper bound	Range
Cost - uncontrolled asthma	£25,458	£25,359	£99
% early non responders - reslizumab	£25,338	£25,477	£139
Percentage of females	£25,480	£25,331	£149
Cost - moderate exacerbation	£25,485	£25,332	£153
Utility - uncontrolled asthma	£25,314	£25,503	£188
Utility - moderate exacerbation	£25,295	£25,523	£228
Utility - severe exacerbation	£25,274	£25,544	£271
Cost - controlled asthma	£25,244	£25,572	£328
% moderate – reslizumab	£25,575	£25,243	£333
% moderate - BSC	£24,547	£26,313	£1,766
Utility - controlled asthma	£26,386	£24,342	£2,044
% severe --> hospitalisation	£26,980	£24,133	£2,847
Cost - severe exacerbation	£23,016	£26,386	£3,369
Weight	£23,123	£26,565	£3,443
Patient age	£27,251	£23,614	£3,638
Discount rate	£22,352	£26,688	£4,336
Cost - severe exacerbation	£27,800	£23,016	£4,784
OR asthma death	£28,568	£22,234	£6,334
Time horizon	£38,407	£25,408	£12,999
BSC annual rate of exacerbations	£33,660	£19,744	£13,916

OR: Odds Ratio ; BSC: Best Standard of Care

3.1.3 Probabilistic sensitivity analysis

Results of the PSA are presented in Figure 2 and Figure 3. Reslizumab was associated with probabilities of cost-effectiveness of 34% and 67% at thresholds of £20,000 and £30,000 respectively.

Figure 2. Cost-effectiveness place: PSA results

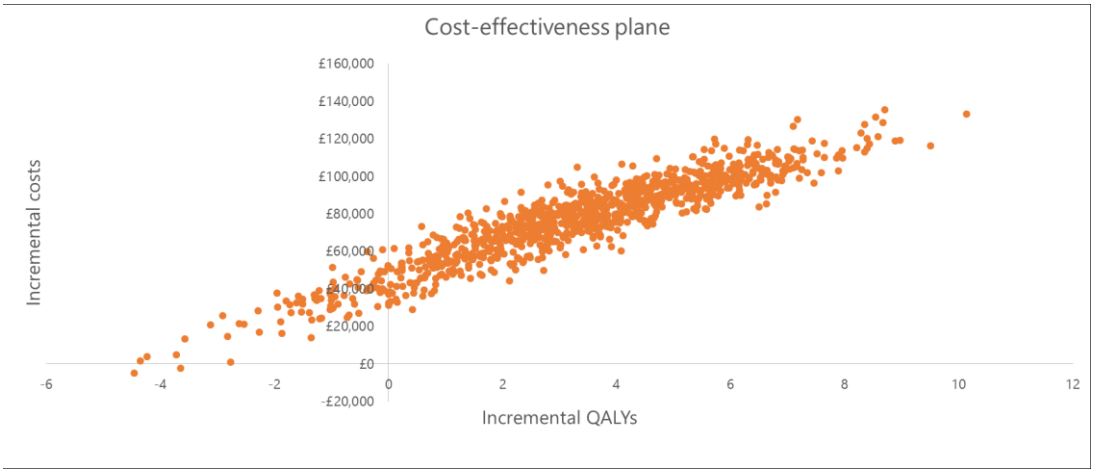
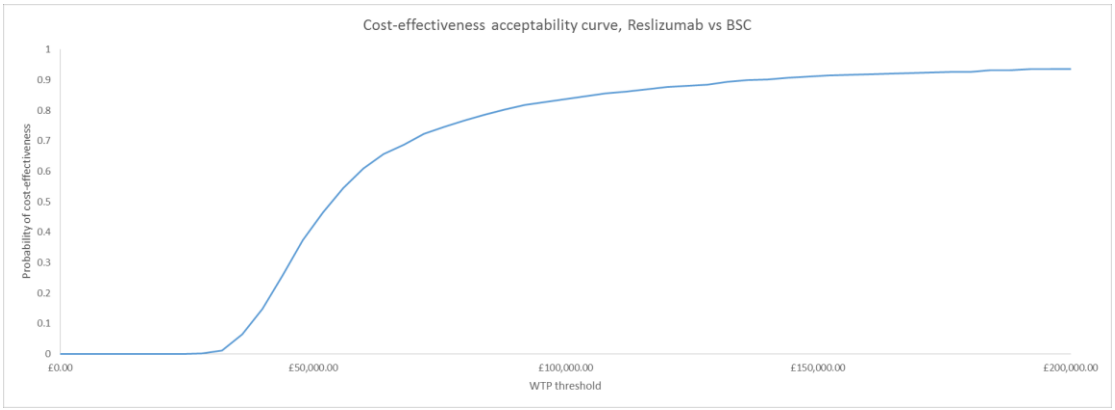


Figure 3. Cost-effectiveness acceptability curve



3.2 Scenario analyses

3.2.1 Scenario analysis: 100 mg vials

The impact of using 100-mg vials instead of 25 mg vials was assessed. Results are presented in

Table 6. The incremental costs were found to increase from £78,462 to £105,572 resulting in a cost per QALY gained of £33,753. Assuming vial sharing, the ICER would decrease to £23,483.

Table 6. Scenario analysis: 100mg vials

	Total costs			Total QALYs			ICER
Scenario	Reslizumab	BSC	Incremental	Reslizumab	BSC	Incremental	
Base-case: 25 mg vials	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,408
Scenario analysis: 100 mg vials	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£34,187
Scenario analysis: 100 mg vials, vial sharing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,483

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

3.2.2 Scenario analysis: Vial-based dosing

Using VBD, the incremental costs was found to decrease from £78,462 to £67,945 resulting in a cost per QALY gained of £22,003.

Table 7. Scenario analysis: VBD

	Total costs			Total QALYs			ICER
Scenario	Reslizumab	BSC	Incremental	Reslizumab	BSC	Incremental	
Base-case: 25 mg vials	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,408
Scenario analysis: 100 mg vials	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,003

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

3.2.3 Scenario analysis in the subgroup of patients with ≥4 exacerbations

A scenario analysis focusing on the subgroup of patients with ≥4 exacerbations in previous year was run. The mean number of exacerbations within this cohort of patients was found to be [redacted] The model was calibrated to match this number. Results are presented in Table 8.

Within this population reslizumab was found to be associated with a cost per QALY gained of £19,457.

Table 8. Subgroup analysis ≥4 exacerbations in previous year

Scenario	Total costs			Total QALYs			ICER
	Reslizumab	BSC	Incremental	Reslizumab	BSC	Incremental	
Base-case: ≥ 3 exacerbations in previous year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,408
Subgroup of patients with ≥ 4 exacerbations in previous year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,457

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

Additional scenario analyses were run for the subgroup of patients with ≥4 exacerbations in previous year:

Table 9. Subgroup analysis ≥4 exacerbations in previous year

Scenario	Total costs			Total QALYs			ICER
	Reslizumab	BSC	Incremental	Reslizumab	BSC	Incremental	
Subgroup of patients with ≥ 4 exacerbations in previous year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,457
Subgroup of patients with ≥ 4 exacerbations in previous year, 100 mg vials	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,525
Subgroup of patients with ≥ 4 exacerbations in previous year, no adjustment to real world evidence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£40,715

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

Results of the probabilistic sensitivity analysis in the subgroup of patients with ≥4 exacerbations are presented in Figure 4 and Figure 5. Reslizumab was associated with probabilities of cost-effectiveness of respectively 63% and 84% at willingness-to-pay thresholds of £20,000 and £30,000.

Figure 4. Cost-effectiveness place: PSA results, 4+ exacerbations

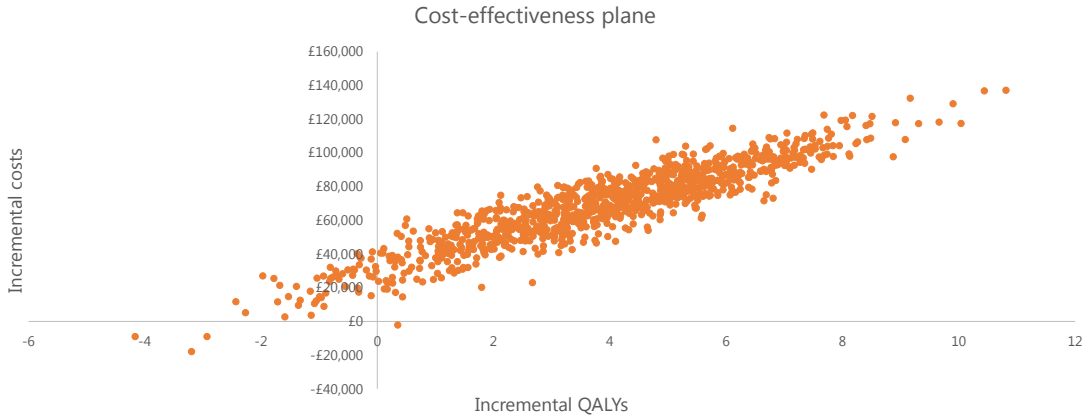
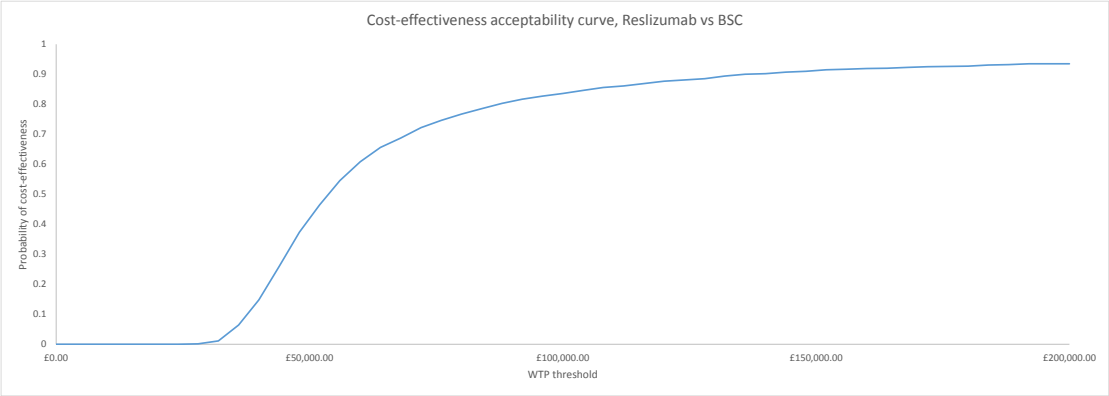


Figure 5. Cost-effectiveness acceptability curve: 4+ exacerbations



Reslizumab was associated with probabilities of cost-effectiveness of 63% and 84% at willingness-to-pay thresholds of £20,000 and £30,000 respectively.

3.2.4 Scenario analyses: no adjustment of rate of exacerbations to clinical practice

A scenario analysis based on the transition probabilities observed in the clinical trial without any adjustment to reflect the rate of exacerbations observed in clinical practice was run. In this scenario, the predicted rate of exacerbations at 1 year in the BSC arm was 2.68.

Table 10. No adjustment of rate of exacerbations to clinical practice

Scenario	Total costs			Total QALYs			ICER
	Reslizumab	BSC	Incremental	Reslizumab	BSC	Incremental	
Base-case: ≥ 3 exacerbations in previous year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,408
No adjustment to real world rate of exacerbations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£43,064

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

3.2.5 Scenario analyses using assessment of response at 6 months

Three scenarios were 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

The results are presented in the following table. The two scenarios resulted in the same results, with an ICER that was very similar to the base-case analysis, £24,384 per QALY gained.

Table 11. Scenario analysis: response assessment at 6 months

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

4 Appendix

4.1 Transition probabilities

The transition probabilities that are used in the updated base case analysis are reported below.

Table 3. BSC transition probabilities estimated based on patients with 3+ exacerbations.

		Health state visit (i+1)			
		Controlled	Uncontrolled	Moderate exacerbation	Severe exacerbation
Health state visit (i)	Controlled	0.7103	0.2255	0.0117	0.0525
	Uncontrolled	0.1812	0.7069	0.0204	0.0915
	Moderate exacerbation	0.2667	0.5654	0.0306	0.1373
	Severe exacerbation	0.2667	0.5654	0.0306	0.1373

The transition probabilities for reslizumab are reported below and relate to:

1. All patients initiating treatment from week 0 to 16 (applied from initiation to the assessment of response for continuation of treatment, i.e. weeks 0 to 16)
2. The population excluding early non responders (11.1% in the subgroup of patients with 3+ exacerbation), which apply from week 16 to 52 as early non responders discontinue treatment at 16 weeks in the base case analysis.
3. The responders who continue treatment beyond one year.

Table 12. Reslizumab transition probabilities estimated based on patients with 3+ exacerbations.

a) Week 0 to 16

		Health state visit (i+1)			
		Controlled	Uncontrolled	Mod. exacerbation	Sev. exacerbation
Health state visit (i)	Controlled	0.743	0.257	0.000	0.000
	Uncontrolled	0.280	0.583	0.032	0.104
	Mod. exacerbation	0.125	0.688	0.044	0.143
	Sev. exacerbation	0.125	0.688	0.044	0.143

b) Week 16 to 52

		Health state visit (i+1)			
		Controlled	Uncontrolled	Mod. exacerbation	Sev. exacerbation
Health state visit (i)	Controlled	0.859	0.111	0.007	0.023
	Uncontrolled	0.213	0.742	0.011	0.034
	Mod. exacerbation	0.450	0.450	0.024	0.076
	Sev. exacerbation	0.450	0.450	0.024	0.076

c) From week 52

		Health state visit (i+1)			
		Controlled	Uncontrolled	Mod. exacerbation	Sev. exacerbation
Health state visit (i)	Controlled	0.869	0.104	0.006	0.021
	Uncontrolled	0.252	0.727	0.005	0.016
	Mod. exacerbation	0.600	0.400	0.000	0.000
	Sev. exacerbation	0.600	0.400	0.000	0.000

4.2 Cost of administration

During the initial visits additional monitoring time may be required so that the 15 minutes assumed for regular administration visits may be underestimated. Assuming 30 minutes of monitoring, the total preparation, administration and monitoring time would then amount to 80 minutes at £79.62 for the first administrations.

In addition, the first administration of reslizumab also requires cannula insertion. The cost of cannula insertion was estimated based on calculations from a NICE costing template for a different condition as £28.50 (inflated to 2016), as follows:

Table 13. Cost of cannula insertion.

Registrar -10 minutes	£10.33	PSSRU -Curtis 2011 – 1 hour £62
Band 5 nurse - 10 minutes	£6.67	PSSRU - Curtis 2011 – 1 hour £40
Consumables - cannula	£6.97	Consumables costs – see source
Total	**£23.97**	
Inflated to 2016 at 3.5%	**£28.50**	

The following NHS reference HRGs apply to day case treatment of asthma:

Table 14. HRG tariffs related to asthma

HRG Code	Description	National Avg	Lower QT	Upper QT
DZ15M	Asthma with Interventions	£583	£501	£501
DZ15N	Asthma without Interventions, with CC Score 9+	£495	£534	£534
DZ15P	Asthma without Interventions, with CC Score 6-8	£466	£571	£571
DZ15Q	Asthma without Interventions, with CC Score 3-5	£347	£440	£440
DZ15R	Asthma without Interventions, with CC Score 0-2	£316	£438	£438

The HRG DZ15R was selected for the base case analysis. While severe asthma would typically be associated with higher comorbidity and complexity (CC) scores, costs associated with intravenous administration of a drug and subsequent monitoring do not depend on comorbidities. Comorbidity and complexity score would impact costs of initial assessment, for which two day case admissions are required, but such assessment costs would be similar for reslizumab and for best standard of care. Therefore the lowest cost estimate of £316 was deemed most appropriate. Relative to the previous microcosting estimate of £79.62 with the added cost of cannula insertion (£28.50), the £316 cost of HRG DZ15R for the first three administration of reslizumab is conservative as it would allow for over 3 hours of specialist nurse time.

References

1. National Institute for Health and Care Excellence. Reslizumab for treating eosinophilic asthma inadequately controlled by inhaled corticosteroids 2016 [Available from: https://www.nice.org.uk/guidance/GID-TA10036/documents/appraisal-consultation-document.
2. Price D, Wilson AM, Chisholm A, Rigazio A, Burden A, Thomas M, et al. Predicting frequent asthma exacerbations using blood eosinophil count and other patient data routinely available in clinical practice. J Asthma Allergy. 2016;9:1-12.
3. National Institute for Health and Care Excellence. Guide to the Methods of Technology Appraisal 2013. NICE Process and Methods Guides. London2013.
4. Meyers A. Final Study Report: Burden of Disease in People with Severe, Uncontrolled Asthma: A Retrospective Chart Review Study. IPSOS Healthcare. 2016.
5. Niven RM, Saralaya D, Chaudhuri R, Masoli M, Clifton I, Mansur AH, et al. Impact of omalizumab on treatment of severe allergic asthma in UK clinical practice: a UK multicentre observational study (the APEX II study). BMJ Open. 2016;6(8):e011857.
6. Sweeney J, Brightling CE, Menzies-Gow A, Niven R, Patterson CC, Heaney LG, et al. Clinical management and outcome of refractory asthma in the UK from the British Thoracic Society Difficult Asthma Registry. Thorax. 2012;67(8):754-6.
7. Gibeon D, Heaney LG, Brightling CE, Niven R, Mansur AH, Chaudhuri R, et al. Dedicated severe asthma services improve health-care use and quality of life. Chest. 2015;148(4):870-6.
8. European Medicines Administration. Summary of Product Characteristics: CINQAERO 10 mg/mL concentrate for solution for infusion [Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003912/WC500212250.pdf.
9. GOV.UK. NHS reference costs 2014 to 2015 2015 [Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015.
10. Food and Drug Administration. FDA Briefing Document - BLA 761033: Reslizumab for intravenous injection to reduce exacerbations, relieve symptoms, and improve lung function in adults and adolescents (12 years of age and above) with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids 2015 [Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM475759.pdf.
11. National Institute for Health and Care Excellence. Single Technology Appraisal: Reslizumab for treating eosinophilic asthma inadequately controlled on inhaled corticosteroids [ID872] - Committee Papers 2016 [Available from: https://www.nice.org.uk/guidance/GID-TA10036/documents/committee-papers.
12. Norman G, Faria R, Paton F, Llewellyn A, Fox D, Palmer S, et al. Omalizumab for the treatment of severe persistent allergic asthma: a systematic review and economic evaluation. Health Technol Assess. 2013;17(52):1-342.
13. Murphy K, Garin M, Bardin P. Effect Of Reslizumab Treatment On Rescue Systemic Corticosteroid Use In Patients With Asthma And Elevated Blood Eosinophils:

Results From A Pooled Analysis Of Two Phase 3, Placebo-Controlled Trials. A39 EOSINOPHILIC AIRWAYS DISEASE: Am Thoracic Soc; 2016. p. A7783-A.
14. ClinicalTrials.gov. An Efficacy and Safety Study of Reslizumab Subcutaneous in Patients With Oral Corticosteroid Dependent Asthma and Elevated Blood Eosinophils 2016 [Available from: https://clinicaltrials.gov/ct2/show/NCT02501629.

Asthma UK response to NICE's appraisal consultation document on reslizumab for treating eosinophilic asthma inadequately controlled on inhaled corticosteroids

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.

1. Has all of the relevant evidence been taken into account?

Asthma UK considers reslizumab to be a novel and innovative treatment that could help to address a significant unmet need for people with severe eosinophilic asthma, and we note that the committee agrees that these patients need alternative treatment options to those presently available.

The committee has highlighted an evidence gap on the overall costs of oral corticosteroid (OCS) use, and how reslizumab may impact on these. As both patient experts expressed at the committee meeting, use of OCS is a key concern for people with severe asthma due to the serious side-effects these can have as a result of frequent use over the long term. As one of the very few treatments options available to treat severe asthma, people almost always find themselves taking very high doses of these medicines for a long time and so these serious side effects are common in this group.

A recent study by Sweeney et al. has attempted to fill some of this evidence gap on comorbidities resulting from severe asthma requiring OCS.[1] This is a recent study, published online earlier this year, which 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. The paper has been described as "the best estimate yet of the burden of OCS treatment in severe asthma".[2]

Estimating the impact of the effects of OCS use is a crucial area that needs to be addressed, particularly given that from a patient perspective, reduced use is a key benefit of any future treatment. The long term treatment costs of other conditions caused by OCS use should therefore be considered in the cost-effectiveness analysis of new treatments. There remains a significant gap in high quality data that considers the morbidity due to OCS use, however the paper by Sweeney et al provides some basis to aid estimates of the effects of OCS use to help ensure this is included in modelling of the incremental cost-effectiveness ratio (ICER).

2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes.

3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

While we are disappointed that the committee is not yet in a position to feel it can recommend reslizumab, we hope that the additional information the committee has requested will enable it to

---

[1] Sweeney J, Patterson CC, Menzies-Gow A, 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.

[2] Choo XN, Pavord ID. Morbidity associated with oral corticosteroids in patients with severe asthma. Thorax 2016;71:4 302-304

reach a position where this treatment can be recommended to people with severe eosinophilic asthma.

Additional comments

Similar challenges are being faced in the reslizumab appraisal as we seen in the mepolizumab appraisal and we urge NICE and all industry to work together to improve submissions for single technology appraisals.

Please contact , Senior Policy Officer, at if you have any questions related to this response.

British Thoracic Society

17 Doughty Street, London WC1N 2PL
T: +44 (0) 20 7831 8778 F: +44 (0) 20 7831 8766
bts@brit-thoracic.org.uk
www.brit-thoracic.org.uk
Registered as a charity in England and Wales No. 285174
Scottish Charity No. SC041209
Company Registration No. 1645201

To be submitted via NICE docs

December 2016

Dear Sir,

ACD - Consultees & Commentators: Asthma (eosinophilic) - reslizumab (after inhaled corticosteroids) [872]

Thank you for inviting comments from the British Thoracic Society on the Appraisal Consultation Document (ACD).

We note the recommendations contained in the ACD. In particular:

1. No data are included on exacerbation prone patients, or reduction in exacerbations in these patients. This study is ongoing and we believe due to finish collecting data end of next year.

2. Steroid reduction: again this study is currently ongoing and due to finish collecting day end of next year.

These data would be needed to compare reslizumab to mepolizumab.

3. Dosage and administration- to be considered along side mepolizumab, data are needed on fixed dosage and subcut administration. The point on wastage from 100mg vials is valid. For a 70kg person, the cost si comparable to mepolizumab, but at heavier weights, the cost would be much higher.

If the MENSA and SIRIUS equivalent studies are projected to have data out by 2018, it would seem appropriate that the next review of reslizumab is after that. However, by then we hope there would be more data on real life use of mepolizumab which could be used in comparison.

Yours faithfully,

Royal College of Physicians
11 St Andrews Place
Regent's Park
London NW1 4LE
Tel: +44 (0)20 3075 1560

www.rcplondon.ac.uk

[redacted]

National Institute for Health and Care Excellence
1st Floor
10 Spring Gardens
London
SW1A 2BU
TACommA@nice.org.uk

29 November 2016

Dear Sir or Madam

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

The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 33,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

The RCP is grateful for the opportunity to respond to the above consultation. We have liaised with experts in immunology and allergy and respiratory medicine and would like to make the following comments.

Our experts believe it is reasonable that the company needs to recalculate its cost-benefit analysis with different parameters, especially in terms of administrative costs and placebo effects. The ACD makes the point that the likely target group in the UK will be different from the groups included in the trials. This is not easily fixable. Furthermore, reslizumab has a direct competitor (mepolizumab) which is also an anti-IL-5 antibody and which works in exactly the same way, and has parketing authorisation as Nucala.

Our experts question why there is no mention of the GSK product (Nucala) and its supporting data in the ACD but note that this may be a technical issue of how NICE works. Our experts believe that both monoclonal anitbodies will be used for the same group of patients. This is a small but deserving subset of patients who get a lot of side-effects form their current therapy (long term systemic glucocorticosteroids). Our experts note concern that mepolizumab and reslizumab will be used indiscriminately.

Our experts believe that the key to this is coordination of care within networks. There is some vagueness in the ACD about the definition of specialist centres - ideally these patients should be treated locally. Their care should be approved and monitored by regional MDTs and there should be registries run by the specialist centres. That is not the same as delivering the care in specialist centres. Our experts believe that physicians should avoid blanket support for a system of specialist centres which makes it difficult for patients across the country to access care if they do not live near to a centre.

Our experts note that these monoclonal antibody therapies are expensive, but necessary for small numbers of patients with invasive eosinophilia (as opposed to the huge numbers of patients with incidental/benign eosinophila). The key is to ensure that experts, in accredited centres, use sensible inclusion/exclusion criteria for invasive eosinophila.

Yours faithfully

[redacted]

[redacted]

NHS England Response to NICE ACD – Reslizumab for treating eosinophilic asthma inadequately controlled by inhaled corticosteroids

Please find NHS England's response to the ACD –Reslizumab which has been reviewed by the Respiratory CRG

Has all of the relevant evidence been taken into account?
Yes
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
Omalizumab is assessed at 16 weeks despite its primary outcome being decreased exacerbation frequency. It would be helpful to evaluate the responses to new therapies at similar time points. In this case 26 weeks differs from that of Omalizimab. Teva have produced a model based on FEV1 and AQLQ that predicts later treatment response and it is clinically plausible to use a 16 week assessment in this patient population. It is incorrect to state that patients in routine UK clinical practice will have lower eosinophil counts. The most recent study of patients from the BTS severe asthma registry demonstrated that at referral patients had a median eosinophil count of 300 with an inter quartile range of 150-600 (Gibeon et al. Chest 2015; 148: 870-6).
Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
Yes, in general. We welcome the call for evidence to be submitted on how reslizumab may affect OCS usage, as this is a key concern for people with severe asthma due to the side-effects they experience from long-term OCS use.
Any other comments

This product requires IV administration unlike mepolizumab which is SC

There needs to be consistency across of STAs about the accepted number of exacerbations before an additional, novel asthma treatment is considered.

Similarly, there should be consistency in the eosinophilic levels required to be eligible for treatments. There appear to be different levels set by Committee A and B in the appraisals of reslizumab and mepolizumab.

Similar challenges are being faced in the reslizumab appraisal as those in the mepolizumab appraisal and we urge NICE and all industry to work together to improve submissions to NICE.

NOVARTIS

Novartis Pharmaceuticals UK Limited
200 Frimley Business Park
Camberley
Surrey
GU16 7SR

Mr M Boysen
Programme Director, Centre for Health Technology Evaluation
National Institute for Health and Care Excellence
Level 1A, City Tower, Piccadilly Plaza
Manchester
M1 4BT

6th December 2016

Dear Mr Boysen,

NICE Single Technology Appraisal (STA), Reslizumab for treating asthma with elevated blood eosinophils inadequately controlled by inhaled corticosteroids [ID872] - Appraisal consultation document (ACD).

Thank you for your letter dated 8th November 2016 inviting comments on the above Appraisal Consultation Document (ACD), in which omalizumab (manufactured by Novartis) is mentioned.

The following document answers the questions posed by NICE on page 1 of the ACD.

1. **Has all of the relevant evidence been taken into account?**

Novartis considers that the relevant evidence has generally been taken into account by the Appraisal Committee in preparing the provisional recommendations detailed in the ACD. However, we have some observations summarised below.

<u>Reslizumab – drug and administration costs</u>

- Hospital admission costs

Novartis agrees with the ERG, clinical experts and Appraisal Committee that a hospital admission cost for the intravenous infusion should be incorporated into the reslizumab administration costs in the economic model (ACD, section 4.13).

- Vial wastage and vial sharing

Novartis agrees with the Appraisal Committee that vial wastage in the economic modelling should be based on the licensed 100mg vials rather than unlicensed 25mg vials (ACD, section 4.14). We are concerned that the number of reslizumab vials and subsequently the drug costs for reslizumab appear to be underestimated. The required dose for reslizumab is

3mg/kg, therefore, a patient weighing 40kg would require a dose of 120mg, and two vials of 100mg. However, it appears that the model currently assumes that one 100mg vial will be sufficient for a patient weighing 40kg. Similar issues are identified for other weight ranges: ≥66.8-75.1kg, ≥100.4-108.7kg and ≥134 kg.

Additionally, Novartis believes there should to be caution regarding the assumption of vial sharing as the 'Shelf life' section of the reslizumab Summary of Product Characteristics (SmPC) states(1):

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 16 hours at 2°C - 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

- Other administration costs

Novartis does not believe the timing assumptions (ACD, section 4.13) for treatment preparation, administration and monitoring are reflective of UK clinical practice or consistent with the reslizumab SmPC (1). Please find our comments summarised in the table below:

TEVA assumption	**Reslizumab SmPC (1)**	**Novartis response**
Treatment preparation: 10 minutes		We believe that it may require longer than 10 minutes to complete the pre-dose patient monitoring, calculation of the required dose and preparation of the solution for infusion and cannulation of the patient.
Treatment administration: 30 minutes	'Posology and method of administration section of the reslizumab SmPC states (1); *The diluted medicinal product should then be administered as a 20 – 50-minute intravenous infusion through a sterile, non-pyrogenic infusion, single-use, low protein binding filter (0.2 µm).*	We believe the administration time should be increased above 30 minutes.
Post-dose monitoring time: 15 minutes	The 'Undesirable effects' section of the reslizumab SmPC states the following regarding adverse reactions associated with the reslizumab infusion (1); *Acute systemic reactions, including anaphylactic reactions, have been reported in association with reslizumab (see section 4.8). These adverse reactions were observed*	We believe the monitoring time should be increased to at least 20 minutes to be consistent with the SmPC. We anticipate that in clinical practice patients will be monitored for longer than 20 minutes, especially for the initial infusions.

	during or within 20 minutes after completion of the infusion. Patients should be monitored during and for an appropriate time after administration of reslizumab.	

Estimates of Utility

Novartis agrees with the Appraisal Committee that the utility data for the uncontrolled asthma and controlled asthma health states should be mapped from the AQLQ data from the reslizumab clinical studies rather than published literature (ACD, section 4.15).

2. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

Novartis considers the summaries of clinical and cost-effectiveness in the ACD to be, on the whole, reasonable interpretations of the evidence.

We are in agreement with the Appraisal Committee that the overlap between the omalizumab and reslizumab population is very small and that the indirect comparison of reslizumab with omalizumab is highly uncertain and not suitable for decision-making (ACD, section 4.8).

3. **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**

Novartis believes that, if NICE proceeds to a positive recommendation in the future, it should include clear criteria on the following:

- Blood eosinophil level requirement
- Eligible patient population, for example, people who have had at least 4 exacerbation in the previous 12 months with a clear definition for an exacerbation, for example, the exacerbation definition used in reslizumab clinical trials
- Optimisation of standard therapy, with standard therapy clearly defined and a requirement for compliance with standard therapy to be documented prior to reslizumab initiation
- Assessment of response at a suitable time period

4. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?**

Novartis has no comments.

NOVARTIS

5. Response to the manufacturers economic model

Novartis notes several potential minor errors within the manufacturer's submitted economic model; however, given the degree of redacted formulae and the use of dummy data, we are not able to comment on the magnitude of impact associated with these errors. The scope of our review was therefore limited to structural settings and input values only, on which we have no comments beyond those already outlined in this response.

I hope that our comments are of value. If you require clarification on any aspects of our response, please do not hesitate to contact me.

Yours sincerely,

[redacted]

Novartis Pharmaceuticals UK Ltd.

References:

1. Reslizumab Summary of Product Characteristics, August 2016. https://www.medicines.org.uk/emc/medicine/32496 Accessed November 2016.

INSTITUTE FOR LUNG HEALTH
LEICESTER

UNIVERSITY OF LEICESTER

Department of Infection, Immunity and Inflammation
Glenfield Hospital
Groby Road
Leicester LE3 9QP – UK
Tel: +44 (0)116 258 3841
Fax: +44(0)116 250 2787
Email: aw24@le.ac.uk

[redacted]

16.11.2016

Dear Sir or Madam

Re: Response to the Appraisal Consultation document for reslizumab issued November 2016

I agree with the majority of the statements in the appraisal consultation, but I would qualify some of the statements relevant to the expert opinion.

Paragraph 4.3:
I think this paragraph gives an impression that making a diagnosis of eosinophil asthma is more difficult than it is. The gold standard for diagnosing eosinophilic asthma is the presence of an increased number of eosinophils in sputum. Although this test is not routinely undertaken if it is thought essential it can be done in most specialist centres. In the absence of this test there are a number of surrogates, in particular the peripheral blood eosinophil count and the exhaled nitric oxide concentration, which together with a characteristic clinical picture are usually reliable biomarkers of eosinophilic disease. Inhaled corticosteroids can confound the diagnosis, but this can usually be taken into account in longitudinal assessments. Therefore, in day-to-day practice, in a specialist centre, in most cases, it is straightforward to diagnose whether someone has eosinophilic asthma.

Paragraph 4.5 and 4.6.
There is some confusion in these two paragraphs, which impacts on later paragraphs, about the place of biological anti-eosinophil therapies in severe eosinophilic asthma characterized by an exacerbation prone phenotype. Currently eosinophilic asthmatics who are having 3/4 or more exacerbations a year requiring short courses of high dose oral steroids to control their disease are likely to be recommended to take continuous low dose oral steroids (generally 5-15mg/day). This usually controls their disease very well and they no longer have exacerbations. Indeed this treatment is so effective that if they are still getting significant numbers of exacerbations this would lead to an assessment of their adherence and whether the diagnosis was correct. The place of therapies such as reslizumab is to prevent patients requiring continuous oral steroids in the first place. However we have a large pool of patients who are

already on oral corticosteroids for their asthma which means up to 50% of patients with severe eosinophilic asthma are currently on continuous oral steroids. These patients are well controlled with few exacerbations as long as they continue on systemic corticosteroids. Another role for drugs such as reslizumab is therefore to allow us to significantly reduce the dose, or even stop corticosteroids in this group of patients. The indications for reslizumab in people with severe eosinophilic asthma who have been optimized in specialized centres is therefore either:

1) Poor control, despite optimized care in a specialist centre, with 3/4* or more severe exacerbations a year.

OR

2) Patients requiring oral corticosteroids irrespective of the number of exacerbations they have had in the previous 12 months^

*At the moment omalizumab requires 4 or more exacerbations for eligibility and I believe mepolizumab is likely to follow this if approved. If this is the case 4 or more exacerbations would harmonise inclusion criteria between the relevant treatments although I appreciate the clinical trial data for reslizumab may make this difficult to achieve.

^ I appreciate that there is no steroid sparing data for reslizumab.

I hope these comments are helpful

Yours sincerely

CONFIDENTIAL UNTIL PUBLISHED

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

Evidence Review Group critique of additional analyses provided by Teva Pharmaceuticals in response to the NICE Appraisal Consultation

Produced by Southampton Health Technology Assessments Centre

Authors Keith Cooper, Senior Research Fellow, SHTAC
Geoff Frampton, Senior Research Fellow, SHTAC

Correspondence to Dr Geoff Frampton
Southampton Health Technology Assessments Centre
University of Southampton
First Floor, Epsilon House
Enterprise Road, Southampton Science park
Southampton SO16 7NS
www.southampton.ac.uk/shtac

Date completed 19th December 2016

[redacted]

Note: The company's response to the ACD marks CIC data in yellow and AIC data in blue. The ERG has corrected this in the current report so that CIC data are marked in blue and AIC data are marked in yellow, in accordance with the confidentiality checklist provided by the company.

1. Introduction

The first NICE Appraisal Committee Meeting (ACM) for this reslizumab Single Technology Appraisal was held on 18th October 2016. In response to the evidence discussed at the ACM, the NICE Appraisal Committee issued an Appraisal Consultation Document (ACD) recommending that the company (Teva Pharmaceuticals) should provide further information for consideration by NICE at the second ACM.

In this report we provide an independent critique of the additional clinical effectiveness and cost effectiveness evidence and analyses submitted by the company. A summary of the additional information provided by the company is given in Table 1.

As mentioned in the NICE ACD, the British Thoracic Society (BTS)[1] guidelines on asthma were updated in September 2016. The company's ACD Response refers to "BTS GINA step 4" and "BTS GINA step 5". These are equivalent to the steps "High-dose therapies" and "Continuous or frequent use of oral steroids" in the new BTS guidelines.

Table 1. Overview of the additional information provided by the company in comparison to that requested by NICE

Information requested in the ACD	Information provided by the company
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. Any adjustment related to specific subgroups should be fully explained and justified.	Transition probabilities have been updated to be consistent with new unpublished baseline population characteristics and reslizumab efficacy data for [redacted], for subgroups of patients with ≥3 or ≥4 exacerbations in the year preceding enrolment in the pooled pivotal trials 3082 and 3083 (ACD response section 2.1.2). These transition probabilities were amended for the subgroup with ≥4 exacerbations in the previous year by using an exacerbation factor based upon a 'real world' severe asthma cohort to reflect the exacerbation rate observed in clinical practice in this subgroup (ACD Response section 2.1.4).

Appropriate administration costs, including the need to go to hospital for cannula insertion and supervised infusion.	An updated analysis with increased administration costs has been provided (ACD Response section 2.2)
Drug wastage using only the licensed 100 mg vial.	The company has provided the 25 mg vial analysis in the base case and presented the 100 mg vial analysis as a scenario analysis (ACD Response section 2.3).
Evaluation of response to treatment at periods that reflect clinical practice (such as 6 months from the start of treatment).	The company has provided the 16-week response analysis in the base case and presented a 6-months response analysis as a scenario analysis (ACD Response section 2.4).
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.	The company's base case does not incorporate all amendments recommended in the ACD. The ICER of £25,408 is based on the adjustment including 'real world' data. The ICER without this adjustment is £43,064. However, this is for a 25-ml vial size.
The committee recommends that the company also considers how reslizumab may affect oral corticosteroid usage and its consequent	Unpublished information on rescue systemic corticosteroid use was provided from a post hoc analysis in the two pivotal trials 3082 and 3083. However, the company concluded that currently-available data are not robust and did not include steroid sparing in the cost-effectiveness analysis (ACD Response section 2.5).

adverse effects and their costs.	

2. ERG critique of the company's ACD Response

The ERG's critique is provided below, structured to match the order of the sections as they appear in the company's ACD Response. We have also summarised the company's base case (section 3) and we have provided additional analyses to support our preferred base case (section 4).

2.1 Population and transition probabilities

The NICE ACD recommends an updated cost effectiveness analysis on the effect of reslizumab for subgroups of people with ≥3 or with ≥4 exacerbations in the previous year. In order to produce transition probabilities for the ≥3 exacerbations subgroup, the company has presented new data on population characteristics for the subgroup of patients who had ≥3 exacerbations in the previous year and met the criteria for the BTS GINA Steps 4 or 5, using data pooled across the pivotal trials 3082 and 3083 (ACD Response Table 1). The sample sizes of the pooled reslizumab arms and pooled placebo arms are not reported, but the combined sample for both arms comprised [redacted] patients in total. Although using these subgroups breaks the randomisation of the pivotal trials, the population characteristics appear to be similar in the pooled reslizumab and placebo arms.

2.1.2 Efficacy in the target population

The company has presented new 52-week efficacy results pooled from the two pivotal trials for subgroups [redacted] (Table 2 in the ACD Response). These data appear to suggest that reslizumab when compared to placebo resulted in [redacted] in these subgroups. However, the analyses have several limitations: they were post-hoc; they used an unexplained adjustment; the sample sizes for the reslizumab and placebo arms within the exacerbation subgroups are not reported; and the data are confidential so we are unable to verify them.

The company has also presented new 52-week efficacy results, pooled from the two pivotal trials, for subgroups of patients [redacted] (Table 3 in the ACD Response). There are several limitations to these confidential data: it is unclear (not stated) whether the data reported in ACD Response Table 3 are within-group changes in the reslizumab-treated subgroup or changes comparing reslizumab against placebo (sample sizes for patients receiving reslizumab and placebo in the subgroups are not reported); and the analyses are post-hoc.

2.1.3 Transition probabilities

The company has included transition probabilities for patients with ≥3 exacerbations in the previous year as requested by the NICE appraisal committee. The company mentions that the pooled subgroup of patients who had experienced ≥4 exacerbations ([redacted]) was 'insufficient' to estimate transition probabilities in this subgroup. However, no explanation is given as to how this judgement was made. To obtain a transition matrix for the subpopulation with ≥4 exacerbations the company instead made an adjustment based on 'real world' exacerbation rates by changing the exacerbation factor (as explained in ACD Response section 2.1.4).

2.1.4 Rate of exacerbation in the best supportive care arm

The company has provided new 'real world' data on the rate of exacerbations in a severe asthma population. The rationale given by the company is that baseline exacerbation rates in the clinical trials underestimate those in clinical practice (although the NICE appraisal 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).

The 'real world' exacerbation rate data (shown in Figure 1 in the ACD Response) are taken from [redacted]. As such, we are unable to verify them. The company states that the [redacted]

[redacted]

For comparison with the [redacted] data, the company conducted a 'targeted review' to identify studies documenting exacerbation rates in the population of interest. The methods of the review are not reported. Four additional studies were identified (Table 4 in the ACD Response). Confidential data from a report by Meyers et al. are presented, but the report does not correspond to the Meyers et al. reference provided by the company, which is a conference abstract.[2] The data from Meyers et al. cited in Table 4 of the ACD Response are not given in the conference abstract and so we have been unable to verify them. Further data on the mean number of severe exacerbations (6.24) experienced by patients in a subgroup with ≥4 severe exacerbations are cited as being from a study by Niven et al.;[3] however, these are not reported in the Niven et al. paper referenced by the company and so we cannot verify these either. The study by Niven et al.[3] was in a severe IgE-mediated asthma population, not specifically eosinophilic, whilst other studies identified by the company by Sweeney et al.[4] and Gibeon et al.[5] had median baseline eosinophil counts around 300 per μL.

In summary, there is uncertainty around the 'real world' and published exacerbation rate data which the company has presented (Table 4 of the ACD Response) since no review methods or selection criteria are reported and some of the data cannot be verified.

2.2 Administration costs

The NICE ACD recommends appropriate administration costs, including the need to go to the hospital for cannula insertion and supervised infusion. The company increased the administration costs for the first three visits to account for cannula insertion and increased the initial monitoring time by including costs for a day case admission of £316. For subsequent administrations, the company has increased the nursing time by 10 minutes to 65 minutes to allow for more preparation time. The administration costs used by the company seem reasonable to the ERG although we are not able to comment whether the proposed nursing time is clinically valid.

2.3 25 mg and 100 mg vial presentations

NICE requested that the company should include drug wastage using only the licensed 100 mg vial size. The company has submitted a base case analysis using the 25 mg vial size. The company justifies this by stating that the European Medicine Agency has agreed in principle to support 25 mg vials and these are expected to be available soon after the anticipated date of issue of the final NICE guidance. The company has provided scenario analyses using the 100 mg vial size and also a vial-based dosing scheme using 25 mg and 100 mg vial sizes.

2.4 Evaluation of response

The NICE ACD recommends an updated cost effectiveness analysis that evaluates response to treatment at periods that reflect clinical practice (such as 6 months from the start of treatment). The company has provided arguments for keeping their 16-week response analysis in the updated base case and has included the assessment of response at 6 months as a scenario analysis.

The company has provided new evidence of the early response to reslizumab at 16 weeks (Table 6 in the ACD Response). Limitations are that the analysis was post-hoc, based on subgroups, the sample sizes are not reported, and the data are confidential.

2.5 Oral corticosteroid usage

The company has summarised an analysis of pooled data on the number of 'rescue OCS' prescriptions and the total cumulative dose of corticosteroid from the pivotal trials 3082 and 3083, as reported in a poster by Bardin et al. (which the company cites as Murphy et al.[6]). According to the poster, the prescriptions for systemic corticosteroids [redacted]. The analysis excludes maintenance OCS therapy as this was not permitted to vary during the pivotal trials. Limitations of the analysis are that it was post-hoc, based on subgroups, the sample sizes are not reported, and the data are stated to be confidential (although this appears inappropriate as the poster is referenced to a previous meeting).

The company also mentions an ongoing study of the steroid-sparing effect of reslizumab (NCT02501629) but this is currently recruiting and not due to complete until late 2017 and therefore cannot provide relevant data at present.

The company concluded that there is a lack of robust data on the steroid-sparing effect of reslizumab, and for that reason the effect of reslizumab on OCS use has not been included in their updated economic analysis. Published evidence is available on the oral

corticosteroid-sparing effects in eosinophilic asthma of the closely-related drug mepolizumab (Bel et al.[7]) but the company does not mention this in their ACD response.

2.6 Utilities

The company has amended the utility value for the exacerbation health states using the value suggested in scenario 3 in the ERG report. The utility estimate for the severe exacerbation health state has changed from 0.33 to 0.51. The ERG agrees that this is a more appropriate value to use for the severe exacerbation health state.

2.7 Health state costs

The company has amended the costs associated with each health state on the basis of the ERG suggestions as shown in ACD Table 8. We agree that these values are more appropriate for the health state costs.

3. Summary of the company's base case

The company has provided an updated base case analysis and scenario analyses. The ERG has checked these analyses and has replicated them in the company model submitted.

The company's base case analysis is shown in Table 1. This includes changes from the initially submitted model with the PAS price for resilzumab together with the following changes: updated transition probabilities for patients with ≥3 exacerbations in the previous year, adjustment to the exacerbation rate observed in clinical practice in the UK, updated administration time, updated health state costs, and updated utilities. The company shows the impact of these individual changes in Table 9 of the ACD response. The company's base case assumes the use of 25 mg vials.

Table 1. Company's base case

	Total costs			Total QALYs			ICER
Scenario	[redacted]			[redacted]			
Initially submitted model, Patient Access Scheme (PAS) price	[redacted]			[redacted]			£24,907
Combined effects of all amendments	[redacted]			[redacted]			£25,408

BSC: Best Standard of Care; ICER: Incremental Cost-Effectiveness Ratio; PAS: Patient Access Scheme; QALYs: Quality-Adjusted Life Years

The NICE committee requested that the company's additional analyses should not include an adjustment for a placebo effect and drug wastage should use only the licensed 100 mg vial. The company's base case differs from that requested by NICE in that it includes an adjustment to the exacerbation rate and does not include the analysis with 100 mg vials. The company has included these analyses as scenario analyses (ACD response Table 11 and Table 15). These analyses are shown here in Table 2 and Table 3 for patients with ≥3 and ≥4 exacerbations in the previous year.

Table 2 Company's base case and analyses with no adjustment of exacerbation rate and using 100 mg vials for patients with ≥ 3 exacerbations in the previous year

	Total costs			Total QALYs			ICER
Scenario	**Res-lizumab**	**BSC**	**Incre-mental**	**Res-lizumab**	**BSC**	**Incre-mental**	
Base-case: ≥ 3 exacerbations in the previous year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,408
No adjustment to 'real world' rate of exacerbations; 25 mg vials	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£43,064
No adjustment to 'real world' rate of exacerbations; 100 mg vials	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£55,136

Table 3 Company's base case and analyses with no adjustment of exacerbation rate and using 100 mg vials for patients with ≥ 4 exacerbations in the previous year

	Total costs			Total QALYs			ICER
Scenario	**Res-lizumab**	**BSC**	**Incre-mental**	**Res-lizumab**	**BSC**	**Incre-mental**	
Subgroup of patients with ≥ 4 exacerbations in the previous year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,457
Subgroup of patients with ≥ 4 exacerbations in the previous year; no adjustment to 'real	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£40,715

Scenario	Total costs			Total QALYs			ICER
	Res-lizumab	BSC	Incre-mental	Res-lizumab	BSC	Incre-mental	
world' evidence; 25 mg vials							
Subgroup of patients with ≥ 4 exacerbations in the previous year; no adjustment to 'real world' evidence; 100 mg vials	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,287

4. Additional ERG analyses

The exacerbation rate chosen for the analyses has a large impact on the cost-effectiveness results. The choice of 'real-world' data for the exacerbation rate produces results that are similar to those presented in the original company submission where the company increased the exacerbation rate to a rate similar to that seen in the year before treatment started. As discussed in the NICE appraisal committee meeting, the improvement in exacerbation rate in the clinical trial for placebo patients may be due to better management of patients that led to better medication adherence and hence lower exacerbation rates.

The ERG presents a scenario where the exacerbation rate varies over time. At the start of treatment, patients have an exacerbation rate as seen in the clinical trials (reflecting better initial asthma management), i.e. with no adjustment to the exacerbation rate. Over 10 years the exacerbation rate linearly increases to the exacerbation rate of the 'real world' data. The results for this scenario are shown in Table 4 and Table 5 for patients with ≥3 and ≥4 exacerbations in the previous year.

Table 4 ERG analyses with an increase in the exacerbation rate for patients with ≥ 3 exacerbations in the previous year

Scenario	Total costs			Total QALYs			ICER
	Res-lizumab	BSC	Incre-mental	Res-lizumab	BSC	Incre-mental	
Base-case: ≥ 3 exacerbations in the previous year; increasing BSC exacerbation rate; 25 mg vials	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,952
Base-case: ≥ 3 exacerbations in the previous year;	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,471

	Total costs			Total QALYs			ICER
Scenario	Res-lizumab	BSC	Incre-mental	Res-lizumab	BSC	Incre-mental	
increasing BSC exacerbation rate; 100 mg vials							

Table 5 ERG analyses with an increase in the exacerbation rate for patients with ≥ 4 exacerbations in the previous year

	Total costs			Total QALYs			ICER
Scenario	Res-lizumab	BSC	Incre-mental	Res-lizumab	BSC	Incre-mental	
Base-case: ≥ 4 exacerbations in the previous year; increasing BSC exacerbation rate; 25 mg vials	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,439
Base-case: ≥ 4 exacerbations in the previous year; increasing BSC exacerbation rate; 100 mg vials	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,754

References

1. British Thoracic Society. SIGN 153. British guideline on the management of asthma. September 2016. https://www.brit-thoracic.org.uk/document-library/clinical-information/asthma/btssign-asthma-guideline-2016/

2. Meyers A, Sun SX, Nicolai J, Morimoto Y, DiBonaventura M. Burden of Disease of Severe Uncontrolled Asthma: a European Study. Unpublished abstract. Source not stated.

3. Niven RM, Saralaya D, Chaudhuri R, Masoli M, Clifton I, Mansur AH, et al. Impact of omalizumab on treatment of severe allergic asthma in UK clinical practice: a UK multicentre observational study (the APEX II study). BMJ Open. 2016;6(8):e011857

4. Sweeney J, Brightling CE, Menzies-Gow A, Niven R, Patterson CC, Heaney LG, et al. Clinical management and outcome of refractory asthma in the UK from the British Thoracic Society Difficult Asthma Registry. Thorax. 2012;67(8):754-6

5. Gibeon D, Heaney LG, Brightling CE, Niven R, Mansur AH, Chaudhuri R, et al. Dedicated severe asthma services improve health-care use and quality of life. Chest. 2015;148(4):870-6.

6. Murphy K, Garin M, Bardin P. Effect Of Reslizumab Treatment On Rescue Systemic Corticosteroid Use In Patients With Asthma And Elevated Blood Eosinophils: Results From A Pooled Analysis Of Two Phase 3, Placebo-Controlled Trials. A39 EOSINOPHILIC AIRWAYS DISEASE: Am Thoracic Soc; 2016. p. A7783-A (citation as provided by the company).

7. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, Ortega HG, Pavord ID, SIRIUS Investigators. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med 2014;371 (13):1189-97.