NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Teva
   - Asthma UK
   - British Thoracic Society (endorsed by Royal College of Physicians)
   - Novartis

3. **Evidence Review Group Critique prepared by** Southampton Health Technology Assessments Centre

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

SingleTechnology Appraisal

Reslizumab for treating eosinophilic asthma inadequately controlled by inhaled corticosteroids [ID 872]

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Teva	**1. Executive Summary** Teva welcomes the opportunity to respond to the committee's conclusions in the second Appraisal Consultation Document (ACD2). Teva has considered the committee's conclusions and concerns in ACD2 and has taken steps to address the outstanding concerns. This response aims to summarise these and present a revised base case as follows: • Population: Adults with severe eosinophilic asthma and **3 or more exacerbations** in the previous year. • Transition probabilities: **No adjustment of exacerbation rates** for the Best Supportive Care (BSC + placebo IV) arm to reflect the rates observed in clinical practice in the UK resulting in average exacerbation rates per year of 2.68 compared to 4.85 used in the updated base case analysis in Teva response to ACD1. o Teva submits a scenario analysis based on an approach used by the ERG in their critique of Teva's response to ACD1 with the rate of exacerbations increasing linearly from the end of the first year to year 10 of follow-up in order to reach the rate of exacerbation observed in real clinical practice as in the response to ACD1 (4.85). • Following the submission of clinical evidence to the committee in response to ACD1 demonstrating that r**eslizumab significantly decreases the duration of severe exacerbations** ([redacted] days and [redacted] days for reslizumab and BSC + placebo IV, respectively), **the impact on utility** estimates has been included in the revised base case analysis. • **Vial-based dosing** including both 100-mg and 25-mg vials in line with the expected update of Summary of Product Characteristics (SPC) – this eliminates wastage and reduces the average 28-day dose from [redacted] to [redacted] resulting in [redacted] lower overall cost of treatment compared to the base case submitted in response to ACD1 as well as the initial submission. • **Revised Patient Access Scheme** (PAS) with a new confidential price of [redacted] per 100-mg vial and [redacted] for 25-mg vial which is [redacted] compared to base case submitted in response to ACD1 as well as the initial submission. The inclusion of vial-based dosing in the revised base case together with a revised PAS, brings [redacted] total average cost per patient by [redacted] from [redacted], with an annual cost of [redacted] per patient per year compared to the initial submission and updated base case submitted in Teva response to ACD1. Following the committee's conclusions in ACD2, all other inputs and assumptions in the revised base case are the same as in the updated base case submitted in response to the first ACD (ACD1), including 16-week evaluation of response, updated costs of administration, updated costs and utilities by health state. Oral Corticosteroid Sparing (OCS) sparing effect is not included in the revised base case. A review of preceding Technology Appraisals has been conducted to assess the potential impact of the OCS sparing effect on cost-effectiveness of treatments. The incremental cost-effectiveness ratio (ICER) of the revised base case is **£29,870** per QALY gained. Table 1 shows how each amendment impacts ICER. The probabilistic sensitivity analysis (PSA) produced a mean ICER of **£27,509** per QALY gained. This ICER does not account for the likely higher exacerbation rates that adults with severe eosinophilic asthma would experience. A scenario analysis that accounts for such impact, using an	Comments noted. The committee considered all the information submitted by the company. See FAD sections 4.11, 4.12, 4.13 and 4.16.

	approach proposed by the ERG results in an ICER of £17,748 per QALY gained. OCS reduction associated with the initiation of omalizumab resulted in a decrease in the reported base case ICER by between £4,000 and £6,000 per QALY gained. Table 1. Considering the updated cost-effectiveness evidence, the significantly decreased treatment cost per patient, 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 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 with 3 exacerbations or more in the previous year.**	
Teva	***2 Teva's detailed response to the second Appraisal Consultation Document (ACD2)*** ***2.1 Population – 3 or more exacerbations in the previous year*** The revised base case continues to include patient population of adults with severe eosinophilic asthma and 3 or more exacerbations in the previous year. Severe eosinophilic asthma is defined as those patients meeting criteria of what was previously known as British Thoracic Society (BTS) Step 4 or 5. Teva agrees with the committee conclusion that the reslizumab recommendation do not need to mirror that of mepolizumab given its different product characteristics, evidence base and cost-effectiveness. Teva submitted the evidence for this restricted population from the two pivotal clinical trials (3082 and 3083) in its response to ACD1 at 52 weeks (Table 2, page 9) as well as at 16 weeks (Table 6, page 18 of Teva response to ACD1). This evidence has now been submitted for presentation at the upcoming European Respiratory Society (ERS) congress. We are attaching the submitted abstract to our response. This evidence is summarised in Table **2** below. We have also added in appendix detailed descriptive statistics around these figures for the committee and ERG to review. **Table 2.** In its response to ACD1, Teva also submitted similar evidence specifically for a subgroup of [redacted] adults with 3 or more exacerbations in the year preceding trial enrolment who were optimised on treatment with high-dose ICS and another medicinal product for maintenance treatment as per the reslizumab licensed indication. Most of this evidence has now also been submitted for presentation at the upcoming ERS congress and we are attaching the abstract to our response . Detailed descriptive statistics around these figures are added in appendix for the committee and ERG review. ***2.2 Transition probabilities − no adjustment of exacerbation rates***	Comments noted. See FAD sections 4.5 and 4.6.

	The ACD2 states that the committee would have preferred to see results from a model that used the observed (unadjusted) data from the relevant subgroup in the trials to estimate the transition probabilities. This approach had previously been considered as a scenario analysis. As per the committee preference, the revised base case does not include adjustment to reflect the rate of exacerbations observed in clinical practice in the UK. The transition probabilities for reslizumab and BSC + Placebo IV were estimated based on patients who had experienced 3 or more exacerbations in the year preceding enrolment in the two 52-week pivotal clinical trials ([redacted] in both active and placebo arm combined; studies 3082 and 3083). These are the same transition probabilities that were used in the updated analysis submitted in the Teva response to the ACD1 without adjustment. Based on these transition probabilities, the model is effectively using the mean annual exacerbation rate of 2.68. This is slightly lower compared to the mean rate of exacerbations of 2.73 reported in the BSC + Placebo IV arms of the two pivotal trials (studies 3082 and 3083) at 52 weeks for the subgroup of patients with BTS Step 4 or 5 who experienced 3 or more exacerbations in the year preceding enrolment in the trial. The exacerbation rates used in the revised base case are considerably lower than the exacerbation rate used in the updated base case submitted in response to ACD1 of 4.85 that represents observed exacerbation rates in clinical practice in the UK. **Table 3.** Although Teva acknowledges the committee recommendations and has used unadjusted data in its revised base case, Teva believes that the approach used in the revised base case solely using data from the 52-week clinical trials for the exacerbation rates for the BSC + placebo IV arm is conservative. The restricted population of adults with severe eosinophilic asthma who have experienced 3 or more exacerbations in the previous year is likely to experience, on average, a higher rate of exacerbation over subsequent years in clinical practice compared to those observed within a controlled setting of 52-week clinical trials. As indicated in our response to ACD1, a number of studies conducted in the UK demonstrate that severe asthma patients attending specialised centres experience high level of exacerbations: • Gibeon et al. reported the median number of exacerbations before and after treatment optimisation in a specialised asthma centre. Although there was no restriction on the number of exacerbations in the preceding year for patients to be included in the study, the authors reported a median of 1 unscheduled visit, 2 hospitalisations and 3 rescue oral corticosteroid administrations after treatment optimisation, which is much higher than the mean of 2.68 exacerbations considered in the revised base case analysis. • The baseline risk of exacerbations in the updated base case analysis submitted in response to ACD1 was based on an analysis of the [redacted] cohort, which is part of the [redacted] This source was selected as the only identified cohort of patients attending one of the ten specialised asthma centres in the UK for which the rate of exacerbations was available in the specific subgroup of interest (i.e.	Comments noted. See FAD section 4.12 and 4.13

	patients with 3 exacerbations or more), with patients on average experiencing **** exacerbations per year. • The committee noted that only *** of the **** cohort presented with severe eosinophilic asthma and further questioned whether the mean rate of exacerbations of **** was applicable to eosinophilic patients. Since the last committee meeting, new evidence has been generated based on the **** cohort that addresses this question. When considering all patients with a history of exacerbation in the previous year (i.e. with 1 or more exacerbation in the previous year), the data show that patients with severe eosinophilic asthma experienced on average *** exacerbations per year compared to *** for non-eosinophilic patients. These additional results have been submitted for presentation at the upcoming ERS presentation (**********. • New evidence from the ********** cohort study of *** severe asthma patients showed that patients with eosinophil levels of 400 or more had a mean number of OCS exacerbation, emergency room (ER) visits and hospital admissions numerically higher than in patients with less than 400 eosinophils (**********). The additional clinical and economic benefit of reslizumab given the likely higher exacerbation rates that adults with severe eosinophilic asthma would experience is not included in the revised base case. In order to account for the expected rate of exacerbation in clinical practice and its impact on the ICER, Teva has conducted an additional scenario analysis based on the approach used in the additional analyses of the ERG in its critique of the Teva response to ACD1 (page 9−10 of the ERG critique). In this scenario, the rate of exacerbations observed in the BSC + Placebo IV arm of the clinical trials was assumed to apply to BSC for the duration of the trial (i.e. one year) and over the following nine years the exacerbation rate was assumed to increase linearly until reaching the exacerbation rate of the 'real world' data from ** (i.e. ** exacerbations per year) at year 10. The ERG provided the following rationale behind this approach: "as discussed in the NICE appraisal committee meetings, 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". Teva agrees with this rationale. ***2.3 Duration of severe exacerbations*** As already highlighted by Teva in its response to the ACD1 (page 20 of the response to ACD1), additional post-hoc analyses from the pivotal studies showed that reslizumab significantly reduces the length of severe exacerbations in the target population. In the population of patients with severe eosinophilic asthma and 3 or more exacerbations in the previous year, the mean length of a severe exacerbation was reported to be ** days for the reslizumab arm versus ** days for patients on placebo (******), reflecting a total of * versus ** severe exacerbations respectively. This indicates that patients on reslizumab recover quicker from severe exacerbation than patients on BSC + placebo IV with positive impact on their quality of life in these additional ** days. Severe exacerbations are defined as an exacerbation requiring the use of (additional) systemic steroids. Table 4 summarises the descriptive statistics on the duration of exacerbations reported in trials 3082 and 3082. **Table 4.**	Comments noted. See section 4.17 of the FAD.

	In the original submission severe exacerbations were assumed to last for the same duration regardless of treatment arm and the mean utility estimate was of 0.51 as updated in the Teva response to ACD1. In the revised base case analysis, the mean utility associated with the severe exacerbation health state was estimated by treatment to reflect the impact of different length of exacerbation. Table **5** below summarised the new estimates included in the model: **Table 5.** ***2.4 25-mg vial and vial-based dosing (VBD)*** In ACD2, the committee concluded that the 25-mg vial could be considered in the decision-making and that any positive recommendation would only be made based on the availability of this size of vial. The 25-mg vial remains included in the revised base case given the progress with the regulatory process. Compared to the status in the response to ACD1, Teva anticipates the [redacted] opinion from the Committee for Medicinal Products for Human Use (CHMP) as early as [redacted] and the European Commission (EC) decision in [redacted]. Timelines have been updated given that [redacted] in the CHMP Rapporteur Assessment Report received in by Teva in [redacted]. This has allowed Teva to respond to [redacted] within [redacted] instead of the initially planned [redacted], which further increases the probability of [redacted]. As stated during the last response to ACD, as part of the same regulatory process as for the 25-mg vial line extension, Teva is [redacted]. This states the exact number of 100-mg and 25-mg vials to be used for patients according to bodyweight. The introduction of VBD will simplify the process of determining the dose and reduce the time needed to prepare reslizumab. In addition, not only will it eliminate wastage but it will also reduce the total cost of treatment, as patients in each dosing group will receive a dose marginally lower than the 3mg/kg weight-based dosing. A modelling and simulation approach has estimated that the predicted drug exposures and simulated clinical responses on VBD will be comparable to weight-based dosing while maintaining the same efficacy. The VBD scheme is detailed by age group in the appendix (see section 4.1). The introduction of vial-based dosing is associated with a reduction in the overall cost of treatment by [redacted]**%,** yielding annual savings of **£**[redacted] per patient when considering the initial PAS. Considering this update and acceptance of vial-based dosing in the CHMP Rapporteur Assessment Report, the revised base case presented in this response also assumes vial-based dosing (VBD). ***2.5 Revised Patient Access Scheme (PAS)*** While Teva considers that the initial PAS price of reslizumab represented good value for money to the NHS, in order to maintain cost-effectiveness − while making conservative assumptions on the rate of exacerbations in the BSC arm in line with committee preference− a revised PAS has been submitted. The revised PAS includes both 100-mg and 25-mg vials and represents a [redacted]**%** discount compared with the original PAS.	Comments noted. See FAD section 4.16.

	Table 6. The VBD scheme and the revised PAS price significantly reduces the acquisition costs compared to the initial submission as reported in Table 7 below. The inclusion of vial-based dosing in the revised base case together with the revised PAS, reduces the total average cost per patient by **%, from £****** to £******, at an annual cost of £******** less per patient compared with the initial submission. **Table 7.**	Comments noted. See section 4.18 of the FAD.

Teva	**3 Teva's detailed response to the second Appraisal Consultation Document (ACD2)** 3.1 Revised base case 3.1.1 Base-case and impact of each amendment **individually** Table 8 reports the cost-effectiveness results for the revised base case as described above, which is based on the following: • Adults with severe eosinophilic asthma and 3 or more exacerbations in the previous year. • No adjustment of exacerbation rates for Best Supportive Care (BSC + placebo IV) arm to reflect the rates observed in clinical practice in the UK in the base case. • Utility of severe exacerbations estimated by treatment to reflect the significantly shorter duration of severe exacerbations in patients on reslizumab vs BSC + placebo IV. • Vial-based dosing including both 100-mg and 25-mg vials in line with the expected update of SPC. • Revised Patient Access Scheme (PAS) with a confidential price of *** per 100-mg vial and [redacted] for 25-mg vial. Reslizumab is estimated to be associated with additional costs of £65,673 and additional QALYs of +2.20 over the patient lifetime, resulting in an ICER of £29,870. **Table 8.** **3.1.2 Deterministic sensitivity analysis** The following model inputs were varied as part of the deterministic sensitivity analysis (DSA). When confidence intervals were not available from the original source used to estimate the base case value and/or when the source of variability was thought to be beyond the study source, parameters were varied by +20% and –20% compared with the base case estimate. **Table 9, Table 10. Figure 1,2 and 3** **3.2 Scenario analysis** The scenario analysis suggested by the ERG, whereby the rate of exacerbations is assumed to increase linearly from year 2 to reach the real world estimate of 4.85 exacerbations in year 10 was then implemented. The results are summarised in Table 12 below and shows that when assuming that the rate of exacerbation gradually increase to reach the average rate of exacerbations reported in the clinical practice at 10 years, the ICER decreases markedly to levels well below £20,000 per QALY (£17,748). **Table 12**.	Comments noted. See sections 4.11, 4.12, 4.13, 4.16 and 4.18 of the FAD.

Teva	**4.1 Has all relevant evidence been taken into account?**
	Teva considers that the ACD does not take into account all the relevant evidence that is now available for review. Specifically:
	• Teva asks the committee to consider the cost-effectiveness assessment based on the revised PAS, which is presented in this response.
	• The effect of reslizumab on the duration of severe exacerbations and its impact on the cost-effectiveness assessment. This evidence and corresponding cost-effectiveness analyses are presented in this submission.
	• The consideration of vial-based dosing and its impact on the cost-effectiveness assessment.
	• The evidence demonstrating the baseline risk of exacerbations in the clinical practice in the NHS.
	• The potential impact of OCS sparing on the cost-effectiveness assessment
	  ○ As mentioned in the response to ACD1, 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). 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.
	  ○ Preceding technology appraisals submitted to NICE were reviewed in order to assess the magnitude of the impact of OCS sparing on the ICER. In TA278, which assessed omalizumab, accounting for OCS reduction associated with the initiation of omalizumab resulted in a decrease in the reported base case ICER by between £4,000 and £6,000 per QALY gained. The mepolizumab company submission also referred to the same estimates.
	• In addition, other benefits have not been captured in the cost-effectiveness model such as the impact on patients' carers, as acknowledged by the committee (ACD1, page 17 of 29).
	[redacted]
		Comments noted. See sections 4.11, 4.12, 4.13, 4.16, 4.18 and 4.20 of the FAD.

Teva	**4.2 Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Teva does not consider that the provisional recommendations in the ACD2 constitute a suitable basis for guidance to the NHS as there is now additional evidence provided to allow the committee to re-assess the value of reslizumab. We believe the cost-effectiveness assessment should be based on the submitted revised, which takes into account a revised PAS price. Teva welcomes that 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, • Concluded that, compared with BSC placebo IV, reslizumab is effective in reducing the rate of clinically significant exacerbations. The revised base case demonstrates that reslizumab is clinically effective and cost-effective treatment option for severe eosinophilic asthma patients with a history of 3 exacerbations or more in the previous year.	Comments noted. The recommendations in the FAD have changed taking into consideration the relevant updated evidence reviewed by the committee.
Teva	**4.3 Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Teva believes that the summaries of clinical and cost effectiveness of reslizumab versus BSC are reasonable interpretations of the evidence. The only exception is the analysis whereby exacerbation rates in the BSC arm are deemed representative of the target population within the NHS clinical practice. Real world evidence from severe asthma registries indicates considerably higher burden of exacerbations than in the setting of reslizumab clinical trials. However, additional evidence has since been gathered and is presented in this response. Therefore the cost-effectiveness assessment should be based on the revised PAS and VBD scheme.	Comment noted. See FAD sections 4.12, 4.13 and 4.18.

Teva	**4.4 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 ACD2 or relevant issues needing special consideration which have not been highlighted in previous submissions and consultations.	Comment noted.
Novartis	**Has all of the relevant evidence been taken into account?** Novartis has no further comments in addition to those made in the 1st ACD response. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** In line with other consultee comments to the 1st ACD, Novartis considers it appropriate that any reslizumab guidance should be aligned to the mepolizumab guidance in terms of exacerbation and steroid usage requirements (ACD section, 4.7, page 9). The ACD document states that the committee concluded that the 16 week time point for reassessment of reslizumab was appropriate (ACD section 4.13, page 14). The rationale for accepting this is that there is minimal difference in cost effectiveness for reassessment at 16 weeks or 6 months and a consultation comment that 16 week reassessment is used for reassessing patients on other asthma drugs and therefore it would be helpful to use this same reassessment time point for reslizumab The only other treatment with a 16 week reassessment period is omalizumab and this is based on an assessment of response criteria assessed in the omalizumab randomised controlled clinical trials for which there are robust evidence to support. As stated earlier in the ACD document omalizumab and reslizumab have different mechanism of action and for different patient populations therefore using the same assessment time-point criteria for both treatments may not be appropriate. Additionally, the clinical expert highlighted that a 16 week time-point is too early to assess response to reslizumab. Mepolizumab and reslizumab both have the same mechanism of action and therefore it would seem more clinically relevant to have a similar assessment response time to mepolizumab which is 12 months. We are in agreement that recommendations based on the 25mg vial should only be made by NICE if this vial has received regulatory approval (ACD page 15, section 4.17). If the regulatory approval for the 25mg vial is delayed then analyses and recommendations should be based on the 100mg vial. **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Novartis has no comments.	Comments noted. See sections 4.7, 4.14 and 4.16 of the FAD.

	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.	

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
British Thoracic Society	**Has all of the relevant evidence been taken into account?** Yes	Comment noted.
British Thoracic Society	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Yes, however we note that: The weakness for Reslizumab is that there is scant data on effectiveness for oral steroid withdrawal, and the drug is IV and therefore introduces some extra organisational issues around administration compared with other monoclonal antibodies such as Omalizumab with which there have been comparisons in the appraisal document. We disagree with the conclusion (4.5, page 8 and page 20) that previous exacerbations are not a predictor of subsequent exacerbations as this is one of the strongest predictors. We do not agree that reslizumab (or any other anti-eosinophil treatment) is more appropriate for patients with nasal polyps or rhinitis than omalizumab (page 10): there is no evidence for this. Blood eosinophil counts are a reasonably good biomarker for eosinophilic asthma. There is ample evidence (MENSA, Heaney study) supporting this.Although induced sputum differential cell counts are a good indicator of the airway inflammatory phenotype it is not widely available. If eosinophils have been suppressed by steroids the only argument for using an anti-IL-5 treatment is to allow withdrawal of steroids (which are VERY effective at reducing IL-5). Reslizumab would only be attractive if the dosing was simplified and the price was much less than Mepolizumab.	 Comments noted. See section 4.15 of the FAD. Comment noted. See section 4.5 of the FAD. Comment noted. See section 4.9 of the FAD. Comments noted.

Nominating organisation	Comment [sic]	Response
	The lack of comparison with Mepolizumab is unfortunate: it is clearly the comparator drug.	
British Thoracic Society	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** We agree with the recommendation that (at present) Resilizumab is not recommended for use in eosinophilic asthma. We hope that the company concerned will: i) complete its steroid reduction trials ii) provide specific data on exacerbation reduction- this means looking at patients with frequent exacerbations NOT just one in the previous year We recommend that comparison with Mepolizumab is added to the scope and the committee are asked to review their recommendation following comparison with it.	Comments noted. The recommendations in the FAD have changed taking into consideration the relevant updated evidence reviewed by the committee.
Asthma UK	**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. We welcome recognition by the committee that inadequately controlled severe eosinophilic asthma is associated with substantial morbidity (4.1) and that there is a need for alternative treatment options – particularly those treatments that could replace the need for, or reduce the dose of, oral corticosteroids (OCS). We are disappointed that it was not possible to incorporate potential OCS sparing and the costs in treating the effects of long-term OCS use, based on the low proportion of people that participated in studies 3082 and 3083 that were on maintenance OCS courses and the fact that OCS use had been kept constant. At both appraisal committee meetings so far, the patient experts have been clear that OCS use is a key concern for people with severe asthma due to the serious side-effects resulting from long term use. 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. Ultimately, this means the full picture of the best supportive care that reslizumab is compared against is limited in terms of the costs captured through the appraisal – and fails to consider the quality of life impacts and	Comment noted. Comments noted. See sections 4.11, 4.18 and 4.20 of the FAD.

Nominating organisation	Comment [sic]	Response
	the restrictions people experience due to ill health resulting from OCS treatment. OCS, while cheap to prescribe and effective in treating exacerbations, is sub-optimal in terms of the long-term effects on patients and the subsequent costs on care resulting from these effects. The committee agreed that it would have liked to have seen some exploratory analysis around this issue of OCS sparing and the impact on costs related to comorbidities (4.11), as currently this potential benefit of reslizumab has not been taken into account. We have previously highlighted to the committee that one recent study has attempted to fill some of the evidence gap on comorbidities resulting from severe asthma requiring OCS, using data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry.1 We also note that there is existing literature that highlights the steroid-sparing effects of monoclonal antibody treatments for severe eosinophilic asthma (such as mepolizumab), as highlighted by the Evidence Review Group. 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. In light of the fact that additional monoclonal antibodies treating severe asthma will be likely considered by NICE in the coming years, we believe that the final guidance issued by the committee should make a recommendation to the NHS to support an independent programme of research that seeks to fully analyse the potential cost savings to the NHS resulting from reductions in OCS use.	
Asthma UK	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Yes, based on the evidence available to the committee.	Comment noted.
Asthma UK	**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 further consideration will enable it to reach a position where this treatment can be recommended to people with severe eosinophilic asthma. While we accept that there are some limitations to the data presented to the committee, there remains an unmet need for people with severe asthma and we believe that reslizumab is likely	Comments noted. The recommendations in the FAD have changed taking into consideration the relevant updated evidence reviewed by the committee.

Nominating organisation	Comment [sic]	Response
	to play a role in helping to address this alongside other monoclonal antibodies currently in development. As mentioned above, we hope that the committee will also recommend as a priority that the NHS conducts research that fully considers the cost-savings resulting from reduced comorbidities associated with long-term OCS use. This will not only help to fully reflect the impact of OCS use, and the benefits of reduction in the use of OCS, but will ultimately aid NICE in the future when considering similar treatments that have the potential to reduce the need for OCS. Similarly, as these new monoclonal antibody therapies become increasingly available it is essential that their use be monitored to help build the evidence base of their effects on reducing OCS use alongside reducing exacerbations to ensure responsible ongoing use of resources.	
Royal College of Physicians	The RCP is grateful for the opportunity to respond to the above consultation. We would like to endorse the response submitted by the British Thoracic Society.	Comment noted.

Comments received from commentators - None

Comments received from members of the public - None

Response to the 2nd Appraisal Consultation Document (ACD)

Reslizumab for treating eosinophilic asthma inadequately controlled by inhaled corticosteroids

ID 872

Teva UK

24 February 2017

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1 Executive summary

Teva welcomes the opportunity to respond to the committee's conclusions in the second Appraisal Consultation Document (ACD2). Teva has considered the committee's conclusions and concerns in ACD2 and has taken steps to address the outstanding concerns. This response aims to summarise these and present a revised base case as follows:

- Population: Adults with severe eosinophilic asthma and **3 or more exacerbations** in the previous year.
- Transition probabilities: **No adjustment of exacerbation rates** for the Best Supportive Care (BSC + placebo IV) arm to reflect the rates observed in clinical practice in the UK resulting in average exacerbation rates per year of 2.68 compared to 4.85 used in the updated base case analysis in Teva response to ACD1.
    - Teva submits a scenario analysis based on an approach used by the ERG in their critique of Teva's response to ACD1 with the rate of exacerbations increasing linearly from the end of the first year to year 10 of follow-up in order to reach the rate of exacerbation observed in real clinical practice as in the response to ACD1 (4.85).
- Following the submission of clinical evidence to the committee in response to ACD1 demonstrating that **reslizumab significantly decreases the duration of severe exacerbations** ([redacted] days and [redacted] days for reslizumab and BSC + placebo IV, respectively), the **impact on utility** estimates has been included in the revised base case analysis.
- **Vial-based dosing** including both 100-mg and 25-mg vials in line with the expected update of Summary of Product Characteristics (SPC) – this eliminates wastage and reduces the average 28-day dose from [redacted] to [redacted] resulting in [redacted] lower overall cost of treatment compared to the base case submitted in response to ACD1 as well as the initial submission.
- **Revised Patient Access Scheme (PAS)** with a new confidential price of £[redacted] per 100-mg vial and £[redacted] for 25-mg vial which is [redacted] **%** [redacted] compared to base case submitted in response to ACD1 as well as the initial submission..

The inclusion of vial-based dosing in the revised base case together with a revised PAS, brings [redacted] total average cost per patient by [redacted] **%**, from £[redacted] to **£**[redacted], with an annual cost of **£**[redacted] per patient per year compared to the initial submission and updated base case submitted in Teva response to ACD1.

Following the committee's conclusions in ACD2, all other inputs and assumptions in the revised base case are the same as in the updated base case submitted in response to the first ACD (ACD1), including 16-week evaluation of response, updated costs of administration, updated costs and utilities by health state. Oral Corticosteroid Sparing (OCS) sparing effect is not included in the revised base case. A review of preceding Technology Appraisals has been conducted to assess the potential impact of the OCS sparing effect on cost-effectiveness of treatments.

The incremental cost-effectiveness ratio (ICER) of the revised base case is **£29,870** per QALY gained. Table 1 shows how each amendment impacts ICER. The probabilistic sensitivity analysis (PSA) produced a mean ICER of **£27,509** per QALY gained. This ICER does not account for the likely higher exacerbation rates that adults with severe eosinophilic asthma would experience. A scenario analysis that accounts for such impact, using an approach proposed by the ERG results in an ICER of £17,748 per QALY gained. OCS reduction associated with the initiation of omalizumab resulted in a decrease in the reported base case ICER by between £4,000 and £6,000 per QALY gained.

Table 1. Summary of ICERs with each implemented amendment

Scenario	ICER
Base case submitted in response to ACD1	**£25,408**
• No adjustment on exacerbation rate	£43,064
• Revised utilities for severe exacerbation, no adjustment on exacerbation rate	£42,025
• Vial-based dosing, no adjustment on exacerbation rate	£[redacted]
• Revised PAS, no adjustment on exacerbation rate	£[redacted]
Revised base case with all amendments	**£29,870**

Considering the updated cost-effectiveness evidence, the significantly decreased treatment cost per patient, 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 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 with 3 exacerbations or more in the previous year.**

2 Teva's detailed response to the second Appraisal Consultation Document (ACD2)

2.1 Population – 3 or more exacerbations in the previous year

The revised base case continues to include patient population of adults with severe eosinophilic asthma and 3 or more exacerbations in the previous year. Severe eosinophilic asthma is defined as those patients meeting criteria of what was previously known as British Thoracic Society (BTS) Step 4 or 5. Teva agrees with the committee conclusion that the reslizumab recommendation do not need to mirror that of mepolizumab given its different product characteristics, evidence base and cost-effectiveness.

Teva submitted the evidence for this restricted population from the two pivotal clinical trials (3082 and 3083) in its response to ACD1 at 52 weeks (Table 2, page 9) as well as at 16 weeks (Table 6, page 18 of Teva response to ACD1). This evidence has now been submitted for presentation at the upcoming European Respiratory Society (ERS) congress.[1] We are attaching the submitted abstract to our response. This evidence is summarised in Table 2 below. We have also added in appendix detailed descriptive statistics around these figures for the committee and ERG to review.

Table 2. Efficacy from the two pivotal trials (3082 and 3083) for adult patients with BTS Step 4 or 5 who experienced ≥3 exacerbations in the year preceding enrolment in the trial over 16 and 52 weeks

	n	Exacerbation rate reduction	Rate ratio (95%CI)	FEV1 Gain [L] (95%CI)	ACQ-7 Gain (95%CI)	AQLQ Gain (95%CI)
16 weeks						
52 weeks						

In its response to ACD1, Teva also submitted similar evidence specifically for a subgroup of adults with 3 or more exacerbations in the year preceding trial enrolment who were optimised on treatment with high-dose ICS and another medicinal product for maintenance treatment as per the reslizumab licensed indication. Most of this evidence has now also been submitted for presentation at the upcoming

ERS congress and we are attaching the abstract to our response[1]. Detailed descriptive statistics around these figures are added in appendix for the committee and ERG review.

2.2 Transition probabilities – no adjustment of exacerbation rates

The ACD2 states that the committee would have preferred to see results from a model that used the observed (unadjusted) data from the relevant subgroup in the trials to estimate the transition probabilities. This approach had previously been considered as a scenario analysis. As per the committee preference, the revised base case does not include adjustment to reflect the rate of exacerbations observed in clinical practice in the UK.

The transition probabilities for reslizumab and BSC + Placebo IV were estimated based on patients who had experienced 3 or more exacerbations in the year preceding enrolment in the two 52-week pivotal clinical trials ([redacted] in both active and placebo arm combined; studies 3082 and 3083). These are the same transition probabilities that were used in the updated analysis submitted in the Teva response to the ACD1 without adjustment.

Based on these transition probabilities, the model is effectively using the mean annual exacerbation rate of 2.68. This is slightly lower compared to the mean rate of exacerbations of 2.73 reported in the BSC + Placebo IV arms of the two pivotal trials (studies 3082 and 3083) at 52 weeks for the subgroup of patients with BTS Step 4 or 5 who experienced 3 or more exacerbations in the year preceding enrolment in the trial. The exacerbation rates used in the revised base case are considerably lower than the exacerbation rate used in the updated base case submitted in response to ACD1 of 4.85 that represents observed exacerbation rates in clinical practice in the UK.

Table 3. Mean rate of exacerbations in the BSC + Placebo IV arm used in the model (for adults with severe eosinophilic asthma and 3 exacerbations or more in the previous year)

	Mean annual exacerbation rate
Base case submitted in response to ACD1	4.85
Revised base case predicted by the model – no adjustment	**2.68**
Observed in the clinical trials at 52 weeks*	2.73

*Within a subgroup of patients in two pivotal trials (studies 3082 & 3083) with BTS Step 4 or 5 who experienced 3 or more exacerbations in the year preceding enrolment in the trial

[redacted]

Although Teva acknowledges the committee recommendations and has used unadjusted data in its revised base case, Teva believes that the approach used in the revised base case solely using data from the 52-week clinical trials for the exacerbation rates for the BSC + placebo IV arm is conservative. The restricted population of adults with severe eosinophilic asthma who have experienced 3 or more exacerbations in the previous year is likely to experience, on average, a higher rate of exacerbation over subsequent years in clinical practice compared to those observed within a controlled setting of 52-week clinical trials.

As indicated in our response to ACD1, a number of studies conducted in the UK demonstrate that severe asthma patients attending specialised centres experience high level of exacerbations:

- Gibeon et al.[2] reported the median number of exacerbations before and after treatment optimisation in a specialised asthma centre. Although there was no restriction on the number of exacerbations in the preceding year for patients to be included in the study, the authors reported a median of 1 unscheduled visit, 2 hospitalisations and 3 rescue oral corticosteroid administrations after treatment optimisation, which is much higher than the mean of 2.68 exacerbations considered in the revised base case analysis.

- The baseline risk of exacerbations in the updated base case analysis submitted in response to ACD1 was based on an analysis of the [redacted] cohort, which is part of the [redacted]. This source was selected as the only identified cohort of patients attending one of the ten specialised asthma centres in the UK for which the rate of exacerbations was available in the specific subgroup of interest (i.e. patients with 3 exacerbations or more), with patients on average experiencing [redacted] exacerbations per year.

- The committee noted that only [redacted] of the [redacted] cohort presented with severe eosinophilic asthma and further questioned whether the mean rate of exacerbations of [redacted] was applicable to eosinophilic patients. Since the last committee meeting, new evidence has been generated based on the [redacted] cohort that addresses this question. When considering all patients with a history of exacerbation in the previous year (i.e. with 1 or more exacerbation in the previous year), the data show that patients with severe eosinophilic asthma experienced on average [redacted] exacerbations per year compared to [redacted] for non-eosinophilic patients. These additional results have been submitted for presentation at the upcoming ERS presentation [redacted][3]

- New evidence from the [redacted] cohort study of [redacted] severe asthma patients showed that patients with eosinophil levels of 400 or more had a mean number of OCS exacerbation, emergency room (ER) visits and hospital admissions numerically higher than in patients with less than 400 eosinophils ([redacted]).

The additional clinical and economic benefit of reslizumab given the likely higher exacerbation rates that adults with severe eosinophilic asthma would experience is not included in the revised base case. In order to account for the expected rate of exacerbation in clinical practice and its impact on the ICER, Teva has conducted an additional scenario analysis based on the approach used in the additional analyses of the ERG in its critique of the Teva response to ACD1 [4] (page 9−10 of the ERG critique). In this scenario, the rate of exacerbations observed in the BSC + Placebo IV arm of the clinical trials was assumed to apply to BSC for the duration of the trial (i.e. one year) and over the following nine years the exacerbation rate was assumed to increase linearly until reaching the exacerbation rate of the 'real world' data from [redacted] (i.e. [redacted] exacerbations per year) at year 10. The ERG provided the following rationale behind this approach: "*as discussed in the NICE appraisal committee meetings, 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*". Teva agrees with this rationale.

2.3 Duration of severe exacerbations

As already highlighted by Teva in its response to the ACD1 (page 20 of the response to ACD1), additional post-hoc analyses from the pivotal studies showed that reslizumab significantly reduces the length of severe exacerbations in the target population. In the population of patients with severe eosinophilic asthma and 3 or more exacerbations in the previous year, the mean length of a severe exacerbation was reported to be [redacted] days for the reslizumab arm versus [redacted] days for patients on placebo ([redacted]), reflecting a total of [redacted] versus [redacted] severe exacerbations respectively. This indicates that patients on reslizumab recover quicker from severe exacerbation than patients on BSC + placebo IV with positive impact on their quality of life in these additional [redacted] days. Severe exacerbations are defined as an exacerbation requiring the use of (additional) systemic steroids. Table 4 summarises the descriptive statistics on the duration of exacerbations reported in trials 3082 and 3082.

Table 4. Duration of severe exacerbation reported in studies 3082 and 3083 (adults with severe eosinophilic asthma and 3 exacerbations or more in the preceding year)

	BSC + Placebo IV	BSC + Reslizumab
Number of exacerbations	[redacted]	[redacted]
Mean	[redacted]	[redacted]
Std	[redacted]	[redacted]
Stderr	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]

BSC: Best Standard of Care; CAE: clinical asthma exacerbation; Std: standard deviation; Stderr: standard error.

In the original submission severe exacerbations were assumed to last for the same duration regardless of treatment arm and the mean utility estimate was of 0.51 as updated in the Teva response to ACD1. In the revised base case analysis, the mean utility associated with the severe exacerbation health state was estimated by treatment to reflect the impact of different length of exacerbation. Table 5 below summarised the new estimates included in the model:

Table 5. Utility by health state used in the model

	Reslizumab	BSC + Placebo IV
Uncontrolled asthma	0.728	
Controlled asthma	0.920	
Moderate exacerbation	0.570	
Severe exacerbation	0.54	0.50

2.4 25-mg vial and vial-based dosing (VBD)

In ACD2, the committee concluded that the 25-mg vial could be considered in the decision-making and that any positive recommendation would only be made based on the availability of this size of vial. The 25-mg vial remains included in the revised base case given the progress with the regulatory process. Compared to the status in the response to ACD1, Teva anticipates the [redacted] opinion from the Committee for Medicinal Products for Human Use (CHMP) as early as [redacted] and the European Commission (EC) decision in [redacted]. Timelines have been updated given that [redacted] in the CHMP Rapporteur Assessment Report received in

by Teva in [redacted]. This has allowed Teva to respond to [redacted] within [redacted] instead of the initially planned [redacted], which further increases the probability of [redacted].

As stated during the last response to ACD, as part of the same regulatory process as for the 25-mg vial line extension, Teva is [redacted]. This states the exact number of 100-mg and 25-mg vials to be used for patients according to bodyweight. The introduction of VBD will simplify the process of determining the dose and reduce the time needed to prepare reslizumab. In addition, not only will it eliminate wastage but it will also reduce the total cost of treatment, as patients in each dosing group will receive a dose marginally lower than the 3mg/kg weight-based dosing. A modelling and simulation approach has estimated that the predicted drug exposures and simulated clinical responses on VBD will be comparable to weight-based dosing while maintaining the same efficacy. The VBD scheme is detailed by age group in the appendix (see section 4.1).

The introduction of vial-based dosing is associated with a reduction in the overall cost of treatment by [redacted]**%,** yielding annual savings of **£**[redacted] per patient when considering the initial PAS.

Considering this update and acceptance of vial-based dosing in the CHMP Rapporteur Assessment Report, the revised base case presented in this response also assumes vial-based dosing (VBD).

2.5 Revised Patient Access Scheme (PAS)

While Teva considers that the initial PAS price of reslizumab represented good value for money to the NHS, in order to maintain cost-effectiveness – while making conservative assumptions on the rate of exacerbations in the BSC arm in line with committee preference– a revised PAS has been submitted. The revised PAS includes both 100-mg and 25-mg vials and represents a [redacted]**%** discount compared with the original PAS.

Table 6. Unit cost of reslizumab

	100-mg vial	25-mg vial
List price	£499.99	£[redacted]
Initial PAS	£[redacted]	£[redacted]
Revised PAS	£[redacted]	£[redacted]

The VBD scheme and the revised PAS price significantly reduces the acquisition costs compared to the initial submission as reported in Table 7 below. The inclusion of vial-based dosing in the revised base case together with the revised PAS, reduces the total average cost per patient by [redacted]**%**, from £[redacted] to **£**[redacted], at an annual cost of **£**[redacted] less per patient compared with the initial submission.

Table 7. Drug acquisition cost comparison – revised PAS

	Cost per 28 days	Annual Cost*	Decrease vs initial base case
Original & updated base case: 25-mg vials and initial PAS	£[redacted]	£[redacted]	
Vial-based dosing and initial PAS	£[redacted]	£[redacted]	[redacted]%
Revised base case: Vial-based dosing and revised PAS	**£[redacted]**	**£[redacted]**	**[redacted]%**

*13 administrations of reslizumab

3 Results

3.1 Revised base case

3.1.1 Base-case and impact of each amendment individually

Table 8 reports the cost-effectiveness results for the revised base case as described above, which is based on the following:

- Adults with severe eosinophilic asthma and **3 or more exacerbations** in the previous year.
- **No adjustment of exacerbation rates** for Best Supportive Care (BSC + placebo IV) arm to reflect the rates observed in clinical practice in the UK in the base case.
- Utility of severe exacerbations estimated by treatment to reflect the **significantly shorter duration of severe exacerbations** in patients on reslizumab vs BSC + placebo IV.
- **Vial-based dosing** including both 100-mg and 25-mg vials in line with the expected update of SPC.
- **Revised Patient Access Scheme (PAS)** with a confidential price of £[redacted] per 100-mg vial and £[redacted] for 25-mg vial.

Reslizumab is estimated to be associated with additional costs of £[redacted] and additional QALYs of +2.20 over the patient lifetime, resulting in an ICER of **£29,870**.

Table 8. Revised base case and impact of each amendment

Scenario	Total costs			Total QALYs			ICER
	Reslizumab	BSC	Incremental	Reslizumab	BSC	Incremental	
Base case submitted in response to ACD1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£25,408**
No adjustment on exacerbation rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£43,064
Utility adjustment for severe exacerbation, no adjustment on exacerbation rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£42,025
Vial-based dosing, no adjustment on exacerbation rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised PAS, no adjustment on exacerbation rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised base case with all amendments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£29,870**

3.1.2 Deterministic sensitivity analysis

The following model inputs were varied as part of the deterministic sensitivity analysis (DSA). When confidence intervals were not available from the original source used to estimate the base case value and/or when the source of variability was thought to be beyond the study source, parameters were varied by +20% and –20% compared with the base case estimate.

Table 9. Inputs varied in the DSA

Parameter	Base case	Range	Source
Time horizon	60	5–60	
Discount rate (costs and QALYs)	3.5%	0–5%	
Proportion of patients identified as early non responders to reslizumab	[redacted]	[redacted]	Base case +/- 5 points
Percentage of females	63%	50.5–75.6%	Base case +/- 20%
Patient age	46.8	37.4–56.2	
Proportion of severe exacerbations leading to hospitalisation	[redacted]	[redacted]	

Proportion of moderate exacerbations (vs severe) - reslizumab	[redacted]	[redacted]	
Proportion of moderate exacerbations (vs severe) - BSC	[redacted]	[redacted]	
Weight expressed as mean number of 25-mg vials: +/-0.5 vials corresponding to a decrease/increase in the weight of 4 kg	[redacted]	[redacted]	Assumption
Cost – controlled asthma	£11.18	£9.49 – £14.23	
Cost – uncontrolled asthma	£45.19	£36.15 – £54.228	Norman et al, 2013
Cost – moderate exacerbation	£70.36	£56.29 – £84.43	
Cost – severe exacerbation	£649.56	£519.65 – £779.47	
Utility – controlled asthma	0.920	0.901–0.943	Lloyd et al, 2007 Willson et al, 2014
Utility – uncontrolled asthma	0.728	0.707–0.749	
Utility – moderate exacerbation	0.57	0.549–0.591	
Average utility of severe exacerbation leading to hospitalization for BSC an reslizumab (based on assumption there is no difference in lengths of exacerbations)	0.33	0.309–0.351	
Reslizumab length of severe exacerbation	[redacted]	[redacted]	Lower and upper bounds of 95% CI in the 3082 and 3083 trials
BSC length of severe exacerbation	[redacted]	[redacted]	
OR – death 25-34	1.1	0.6–0.22	Roberts et al, 2013
OR – death 35-44	1.4	0.7–2.7	
OR – death 45-54	2.4	1.3–4.4	
OR – death 55-64	6.3	3.6–11.1	
OR – death 65+	12.3	7.1–21.3	

Abbreviations: BSC, best standard of care; CI, confidence interval; DSA, deterministic sensitivity analysis; OR, odds ratio; QALY, quality-adjusted life year; RR, relative risk.

Results of the deterministic sensitivity analysis are presented in Figure 1 and Table 10. The time horizon (from 5 to 60 years) was found to be the most influential parameter (ICER ranging from £29,870 to £45,621).

Figure 1. Tornado diagram – deterministic sensitivity analysis

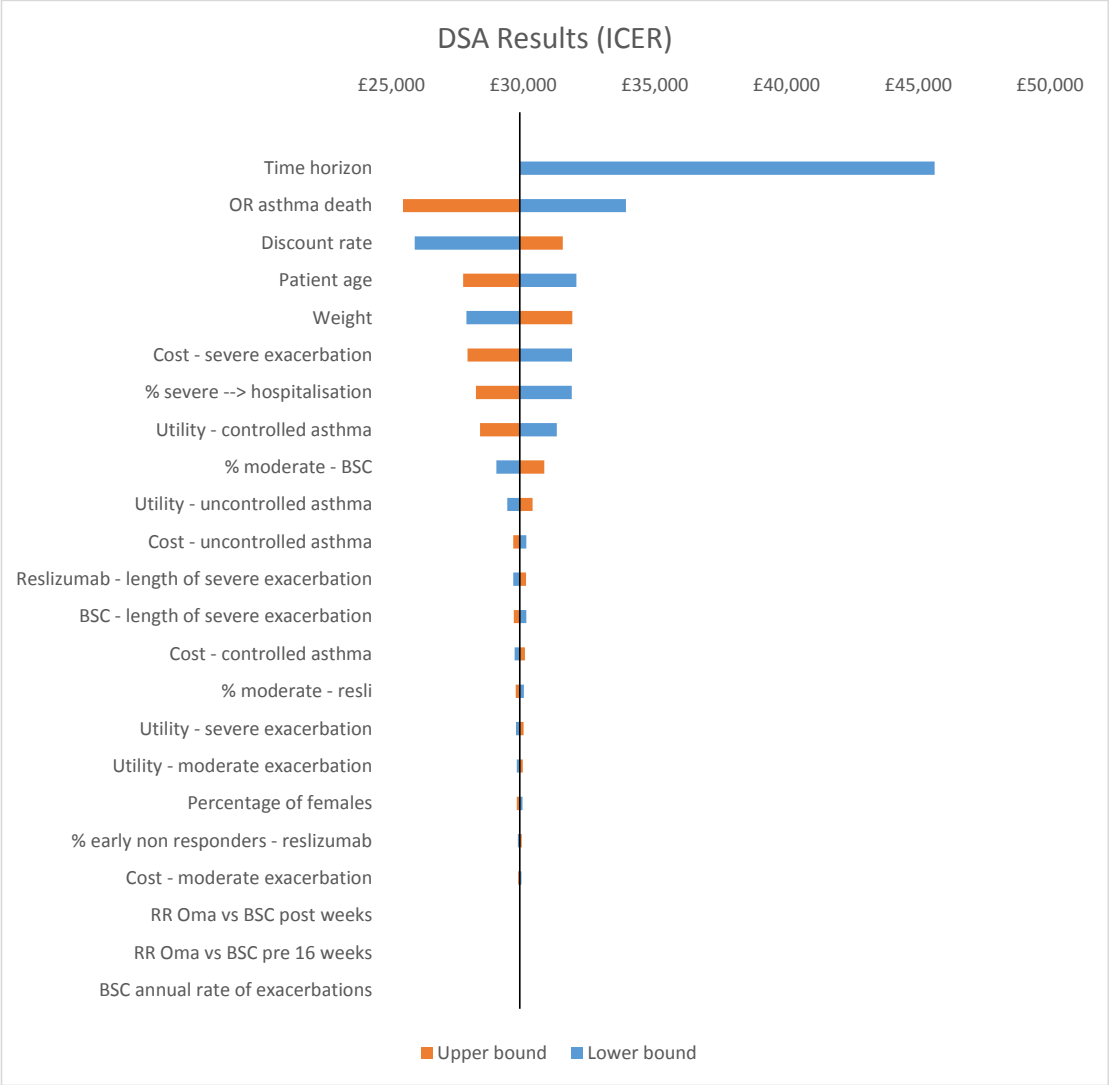


Table 10. Deterministic sensitivity analysis: detailed results

Parameter	ICER Lower bound	ICER Upper bound	Range
Cost - moderate exacerbation	£29,934	£29,806	£127
% early non responders - reslizumab	£29,798	£29,942	£145
Percentage of females	£29,972	£29,760	£212
Utility - moderate exacerbation	£29,759	£29,982	£222
Utility - severe exacerbation	£29,722	£30,020	£298
% moderate - resli	£30,024	£29,717	£308
Cost - controlled asthma	£29,671	£30,069	£398
BSC - length of severe exacerbation	£30,121	£29,648	£473
Reslizumab - length of severe exacerbation	£29,626	£30,111	£486
Cost - uncontrolled asthma	£30,117	£29,623	£494
Utility - uncontrolled asthma	£29,395	£30,361	£966
% moderate - BSC	£28,981	£30,799	£1,818
Utility - controlled asthma	£31,276	£28,362	£2,914
% severe --> hospitalisation	£31,851	£28,211	£3,640
Cost - severe exacerbation	£31,851	£27,889	£3,962
Weight	£27,842	£31,865	£4,022
Patient age	£32,018	£27,725	£4,294
Discount rate	£25,879	£31,509	£5,630
OR asthma death	£33,902	£25,440	£8,461
Time horizon	£45,621	£29,870	£15,751

OR: Odds Ratio; BSC: Best Standard of Care

3.1.3 Probabilistic sensitivity analysis

The details of distributions for each parameter included in the PSA are presented in Table 11.

Table 11. PSA parameter inputs

Parameter	Mean	Alpha (α)	Beta (β)	Distribution
Percentage of females	63%	597	396	Beta

Patient age at model entry	46.80	N/A	N/A	Normal
Mean number of vials	8.59	8.07	9.09	Uniform
Cost of 'Controlled asthma' (cycle)	£11.86	100	0.1186	Gamma
Cost of 'Uncontrolled asthma' (cycle)	£45.19	100	0.4519	Gamma
Cost of 'Moderate exacerbation' (cycle)	£70.36	100	0.7036	Gamma
Cost of 'severe exacerbation' (cycle)	£649.56	100	6.4956	Gamma
Utility of 'Controlled asthma' (cycle)	0.92	464.61	31.24	Beta
Utility of 'Uncontrolled asthma' (cycle)	0.73	2562.04	957.25	Beta
Utility of 'Moderate exacerbation' (cycle)	0.57	1175.32	886.64	Beta
Average utility of severe exacerbation for BSC and reslizumab (based on assumption there is no difference in lengths of exacerbations)	0.33	613.78	1246.17	Beta
Length of severe exacerbation (reslizumab)	[redacted]	[redacted]	[redacted]	Normal
Length of severe exacerbation (BSC + placebo IV)	[redacted]	[redacted]	[redacted]	Normal
% early non responders - reslizumab	[redacted]	[redacted]	[redacted]	Uniform
Proportion of moderate exacerbations (reslizumab)	[redacted]	[redacted]	[redacted]	Uniform
Proportion of moderate exacerbations (BSC + placebo IV)	[redacted]	[redacted]	[redacted]	Uniform
Proportion of severe exacerbations leading to hospitalisation	[redacted]	[redacted]	[redacted]	Uniform
OR death 25-34	1.1	0.05186	0.2948	Lognormal
OR death 35-44	1.4	0.3071	0.24238	Lognormal

OR death 45-54	2.4	0.86714	0.12906	Lognormal
OR death 55-64	6.3	1.82544	0.17383	Lognormal
OR death 65+	12.3	2.50578	0.08736	Lognormal
Reslizumab transition probabilities • Baseline – Week 16 • Week 16 – Week 52 • Post-52 weeks	N/A	N/A	N/A	Beta
BSC transition probabilities • Baseline – Week 52 • Post-52 weeks	N/A	N/A	N/A	Beta

Abbreviations: BSC, best standard of care; N/A, not applicable; OR, odds ratio

Results of the PSA are presented in Figure 2 and Figure 3. Reslizumab was associated with probabilities of cost-effectiveness of 29% and 53% at thresholds of £20,000 and £30,000 respectively. The PSA produced a mean ICER of £27,509/QALY (mean incremental costs of £64,166 over mean incremental QALYs of 2.33) when reslizumab was compared with BSC + placebo IV.

Figure 2. Cost effectiveness plane: Reslizumab vs BSC + placebo IV

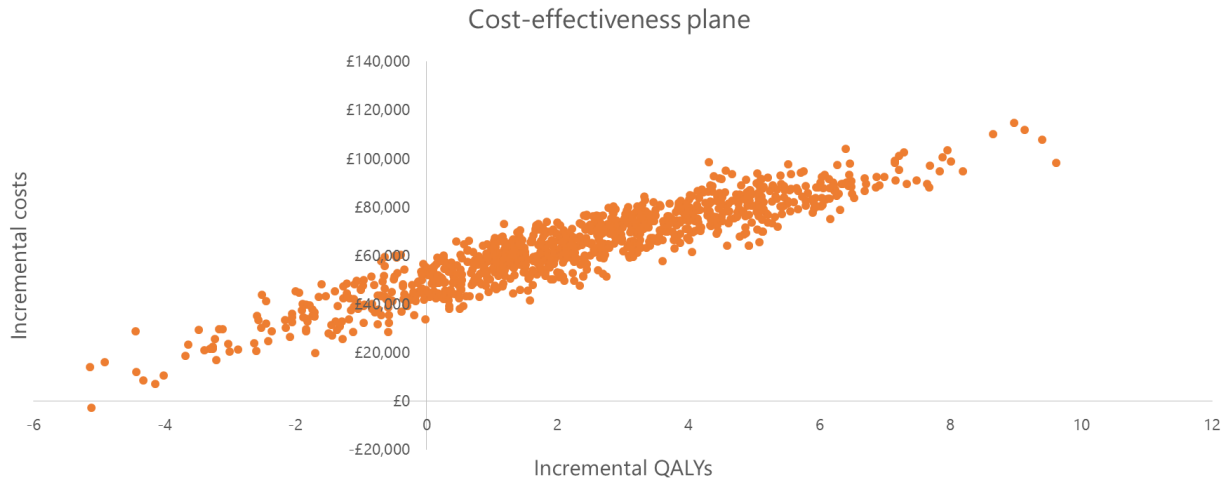
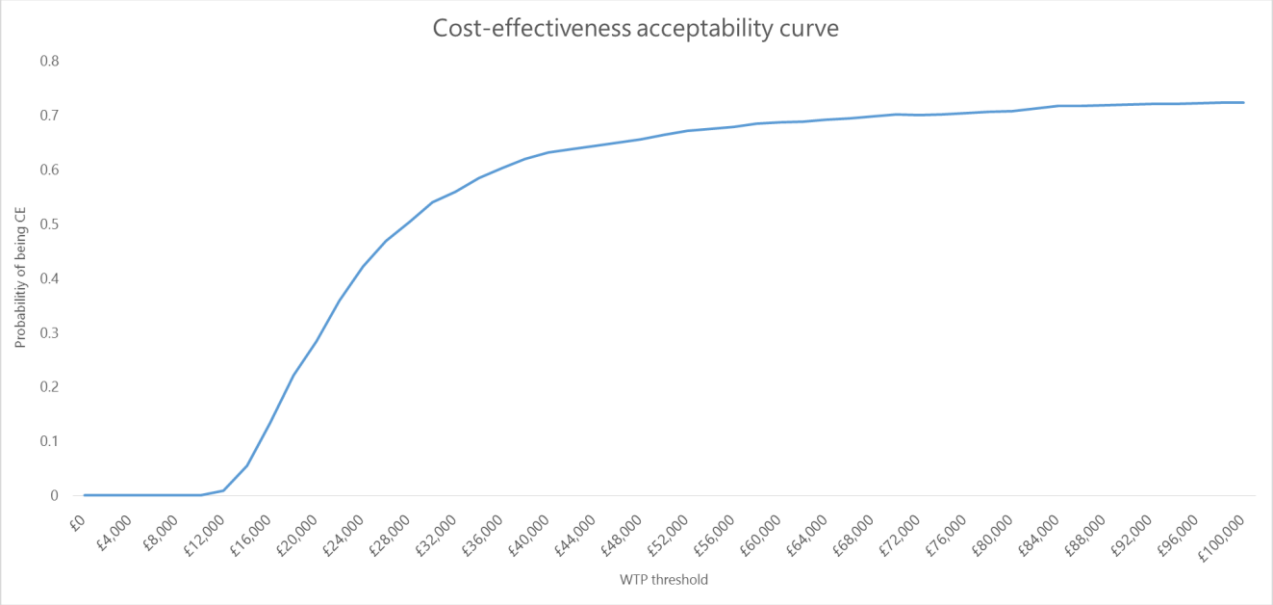


Figure 3. Cost-effectiveness acceptability curve: Reslizumab vs BSC + placebo IV



3.2 Scenario analysis

The scenario analysis suggested by the ERG, whereby the rate of exacerbations is assumed to increase linearly from year 2 to reach the real world estimate of 4.85 exacerbations in year 10 was then implemented.

The results are summarised in Table 12 below and shows that when assuming that the rate of exacerbation gradually increase to reach the average rate of exacerbations reported in the clinical practice at 10 years, the ICER decreases markedly to levels well below £20,000 per QALY (£17,748).

Table 12. Results of scenario analysis: increase in rate of exacerbations over time

	Costs			QALYs			ICER £/QALY
	Reslizumab	BSC + placebo IV	Incremental	Reslizumab	BSC + placebo IV	Incremental	
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,870
Increase in rate of exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£17,748**

4 Overarching questions

4.1 Has all the relevant evidence been taken into account?

Teva considers that the ACD does not take into account all the relevant evidence that is now available for review.

Specifically:

- Teva asks the committee to consider the cost-effectiveness assessment based on the revised PAS, which is presented in this response.
- The effect of reslizumab on the duration of severe exacerbations and its impact on the cost-effectiveness assessment. This evidence and corresponding cost-effectiveness analyses are presented in this submission.
- The consideration of vial-based dosing and its impact on the cost-effectiveness assessment.
- The evidence demonstrating the baseline risk of exacerbations in the clinical practice in the NHS.
- The potential impact of OCS sparing on the cost-effectiveness assessment
    - As mentioned in the response to ACD1, 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 [5]). 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.
    - Preceding technology appraisals submitted to NICE were reviewed in order to assess the magnitude of the impact of OCS sparing on the ICER. In TA278 [6], which assessed omalizumab, accounting for OCS reduction associated with the initiation of omalizumab resulted in a decrease in the reported base case ICER by between £4,000 and £6,000 per QALY gained. The mepolizumab company submission also referred to the same estimates.[7]
- In addition, other benefits have not been captured in the cost-effectiveness model such as the impact on patients' carers, as acknowledged by the committee (ACD1, page 17 of 29).

[redacted]

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

Teva does not consider that the provisional recommendations in the ACD2 constitute a suitable basis for guidance to the NHS as there is now additional evidence provided to allow the committee to re-assess the value of reslizumab. We believe the cost-effectiveness assessment should be based on the submitted revised, which takes into account a revised PAS price.

Teva welcomes that 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,
- Concluded that, compared with BSC placebo IV, reslizumab is effective in reducing the rate of clinically significant exacerbations.

The revised base case demonstrates that reslizumab is clinically effective and cost-effective treatment option for severe eosinophilic asthma patients with a history of 3 exacerbations or more in the previous year.

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

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

However, additional evidence has since been gathered and is presented in this response. Therefore the cost-effectiveness assessment should be based on the revised PAS and VBD scheme.

4.4 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 ACD2 or relevant issues needing special consideration which have not been highlighted in previous submissions and consultations.

5 Appendix

5.1 Vial-based dosing schemes

Table 13: Vial-based dosing scheme

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

*The nominal volume of the vials (10 mL or 2.5 mL for each vial) has to be used.
**Patients weighing more than 188kg were not studied

5.2 Descriptive statistics of efficacy:

5.2.1 3 or more exacerbations in the year preceding trial enrolment

Tables below report all the descriptive statistics of efficacy from the post-hoc analysis of trials 3082 and 3083, for the subgroup of adult patients with BTS Step 4 or 5 who experienced 3 or more exacerbations in the year preceding enrolment in the trial over 16 and 52 weeks.

Table 14. Frequency of exacerbation during treatment period

	Treatment arm (N)	Nb of patients with ≥1 exac. (%)	Mean	SD	SE	Median	Min, Max
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 15. Rate of exacerbations

	Treatment arm (N)	Adjusted rate	95%CI	Rate ratio	95%CI RR	p-value
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<0.0001
	[redacted]	[redacted]	[redacted]			
Week 52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<0.0001
	[redacted]	[redacted]	[redacted]			

Table 16. Change from baseline in AQLQ

	Treatment arm (N)	n	LS mean (SE)	Treatment difference (SE)	95%CI	p-value
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.0284
	[redacted]	[redacted]	[redacted]			
Week 52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.0004
	[redacted]	[redacted]	[redacted]			

Table 17. Change from baseline in FEV1

	Treatment arm (N)	n	LS mean (SE)	Treatment difference (SE)	95%CI	p-value
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.0015
	[redacted]	[redacted]	[redacted]			
Week 52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.0022
	[redacted]	[redacted]	[redacted]			

Table 18. Change from baseline in ACQ-7

	Treatment arm (N)	n	LS mean (SE)	Treatment difference (SE)	95%CI	p-value
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.0009
	[redacted]	[redacted]	[redacted]			
Week 52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.0005

5.2.2 3 or more exacerbations in the year preceding trial enrolment treated with high-dose ICS and another medicinal product for maintenance treatment.

Tables below report all the descriptive statistics of efficacy from the post-hoc analysis of trials 3082 and 3083, for the subgroup of adult patients with BTS Step 4 or 5 and ICS high dose plus another medicinal product for maintenance treatment who experienced 3 or more exacerbations in the year preceding enrolment in the trial at 52 weeks.

Table 19. Change from baseline in FEV1

Treatment arm (N)	n	LS mean (SE)	Treatment difference (SE)	95%CI	p-value
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.0018
[redacted]	[redacted]	[redacted]			

Table 20. Change from baseline in AQLQ

Treatment arm (N)	n	LS mean (SE)	Treatment difference (SE)	95%CI	p-value
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.0016
[redacted]	[redacted]	[redacted]			

Table 21. Change from baseline in ACQ-7

Treatment arm (N)	n	LS mean (SE)	Treatment difference (SE)	95%CI	p-value
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.0103
[redacted]	[redacted]	[redacted]			

Table 22. Change from baseline in ASUI

Treatment arm (N)	n	LS mean (SE)	Treatment difference (SE)	95%CI	p-value
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.0001
[redacted]	[redacted]	[redacted]			

5.3 ERS abstracts:

[redacted]

[redacted]

References

[redacted]

[2] 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

[redacted]

[4] National Institute for Health and Care Excellence. Evidence Review Group critique of additional analyses provided by Teva Pharmaceuticals in response to the NICE Appraisal Consultation [Available from: https://www.nice.org.uk/guidance/GID-TA10036/documents/committee-papers-4

[5] ClinicalTrials.gov. An Efficacy and Safety Study of Reslizumab Subcutaneous in Patients With Oral Corticosteroid Dependent Asthma and Elevated Blood Eosinophils. [Available from: https://clinicaltrials.gov/ct2/show/NCT02501629.

[6] National Institute for Health and Care Excellence. Single Technology Appraisal: Omalizumab for treating severe persistent allergic asthma. Technology appraisal guidance [TA278]. [Available from: https://www.nice.org.uk/guidance/TA278

[7] National Institute for Health and Care Excellence. Single Technology Appraisal: Mepolizumab for treating severe eosinophilic asthma [ID431]. [Available from: https://www.nice.org.uk/guidance/TA431

[redacted]

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

23rd February 2017

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 27th January 2017 inviting comments on the above Appraisal Consultation Document (ACD), in which omalizumab (manufactured by Novartis) is mentioned.

This document answers the four questions posed by NICE on page 1 of the ACD.

Has all of the relevant evidence been taken into account?

Novartis has no further comments in addition to those made in the 1st ACD response.

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

In line with other consultee comments to the 1st ACD, Novartis considers it appropriate that any reslizumab guidance should be aligned to the mepolizumab guidance in terms of exacerbation and steroid usage requirements (ACD section, 4.7, page 9).

The ACD document states that the committee concluded that the 16 week time point for reassessment of reslizumab was appropriate (ACD section 4.13, page 14). The rationale for accepting this is that there is minimal difference in cost effectiveness for reassessment at 16 weeks or 6 months and a consultation comment that 16 week reassessment is used for reassessing patients on other asthma drugs and therefore it would be helpful to use this same reassessment time point for reslizumab

The only other treatment with a 16 week reassessment period is omalizumab and this is based on an assessment of response criteria assessed in the omalizumab randomised controlled clinical trials for which there are robust evidence to support. As stated earlier in the ACD document omalizumab and reslizumab have different mechanism of action and for different patient populations therefore using the same assessment time-point criteria for both treatments may not be appropriate. Additionally, the clinical expert highlighted that a 16 week time-point is too early to assess response to reslizumab. Mepolizumab and reslizumab both have the same mechanism of action and therefore it would seem more clinically relevant to have a similar assessment response time to mepolizumab which is 12 months.

We are in agreement that recommendations based on the 25mg vial should only be made by NICE if this vial has received regulatory approval (ACD page 15, section 4.17). If the regulatory approval for the 25mg vial is delayed then analyses and recommendations should be based on the 100mg vial.

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

Novartis has no comments.

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.

Please do not hesitate to contact me if you require any further information.

Yours sincerely,

[redacted]

Novartis Pharmaceuticals UK Ltd.

Asthma UK works to stop asthma attacks and ultimately cure asthma by funding world leading research and scientists, campaigning for improved care and supporting people with asthma to reduce their risk of a potentially life threatening asthma attack.

Asthma UK
18 Manseli Street
London E1 8AA

0300 222 5800
info@asthma.org.uk
www.asthma.org.uk

Asthma UK response to NICE's second 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. We welcome recognition by the committee that inadequately controlled severe eosinophilic asthma is associated with substantial morbidity (4.1) and that there is a need for alternative treatment options – particularly those treatments that could replace the need for, or reduce the dose of, oral corticosteroids (OCS).

We are disappointed that it was not possible to incorporate potential OCS sparing and the costs in treating the effects of long-term OCS use, based on the low proportion of people that participated in studies 3082 and 3083 that were on maintenance OCS courses and the fact that OCS use had been kept constant. At both appraisal committee meetings so far, the patient experts have been clear that OCS use is a key concern for people with severe asthma due to the serious side-effects resulting from long term use. 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.

Ultimately, this means the full picture of the best supportive care that reslizumab is compared against is limited in terms of the costs captured through the appraisal – and fails to consider the quality of life impacts and the restrictions people experience due to ill health resulting from OCS treatment. OCS, while cheap to prescribe and effective in treating exacerbations, is sub-optimal in terms of the long-term effects on patients and the subsequent costs on care resulting from these effects.

The committee agreed that it would have liked to have seen some exploratory analysis around this issue of OCS sparing and the impact on costs related to comorbidities (4.11), as currently this potential benefit of reslizumab has not been taken into account. We have previously highlighted to the committee that one recent study has attempted to fill some of the evidence gap on comorbidities resulting from severe asthma requiring OCS, using data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry.[1] We also note that there is existing literature that highlights the steroid-sparing effects of monoclonal antibody

[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.

treatments for severe eosinophilic asthma (such as mepolizumab), as highlighted by the Evidence Review Group.[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. In light of the fact that additional monoclonal antibodies treating severe asthma will be likely considered by NICE in the coming years, we believe that the final guidance issued by the committee should make a recommendation to the NHS to support an independent programme of research that seeks to fully analyse the potential cost savings to the NHS resulting from reductions in OCS use.

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

Yes, based on the evidence available to the committee.

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 further consideration will enable it to reach a position where this treatment can be recommended to people with severe eosinophilic asthma. While we accept that there are some limitations to the data presented to the committee, there remains an unmet need for people with severe asthma and we believe that reslizumab is likely to play a role in helping to address this alongside other monoclonal antibodies currently in development.

As mentioned above, we hope that the committee will also recommend as a priority that the NHS conducts research that fully considers the cost-savings resulting from reduced comorbidities associated with long-term OCS use. This will not only help to fully reflect the impact of OCS use, and the benefits of reduction in the use of OCS, but will ultimately aid NICE in the future when considering similar treatments that have the potential to reduce the need for OCS. Similarly, as these new monoclonal antibody therapies become increasingly available it is essential that their use be monitored to help build the evidence base of their effects on reducing OCS use alongside reducing exacerbations to ensure responsible ongoing use of resources.

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

[2] 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.

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

February 2017

Dear Sir,

ACD2 - Reslizumab for treating eosinophilic asthma inadequately controlled on inhaled corticosteroids [ID872]

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

- Has all of the relevant evidence been taken into account? Yes
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes

However we note that:
The weakness for Reslizumab is that there is scant data on effectiveness for oral steroid withdrawal, and the drug is IV and therefore introduces some extra organisational issues around administration compared with other monoclonal antibodies such as Omalizumab with which there have been comparisons in the appraisal document.

We disagree with the conclusion (4.5, page 8 and page 20) that previous exacerbations are not a predictor of subsequent exacerbations as this is one of the strongest predictors.

We do not agree that reslizumab (or any other anti-eosinophil treatment) is more appropriate for patients with nasal polyps or rhinitis than omalizumab (page 10): there is no evidence for this. Blood eosinophil counts are a reasonably good biomarker for eosinophilic asthma. There is ample evidence (MENSA, Heaney study) supporting this.Although induced sputum differential cell counts are a good indicator of the airway inflammatory phenotype it is not widely available.. If eosinophils have been suppressed by steroids the only argument for using an anti-IL-5 treatment is to allow withdrawal of steroids (which are VERY effective at reducing IL-5).

Reslizumab would only be attractive if the dosing was simplified and the price was much less than Mepolizumab.
The lack of comparison with Mepolizumab is unfortunate: it is clearly the comparator drug.

/continued

NICE/BTS February 2017

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

We agree with the recommendation that (at present) Resilizumab is not recommended for use in eosinophilic asthma. We hope that the company concerned will:

i) complete its steroid reduction trials

ii) provide specific data on exacerbation reduction- this means looking at patients with frequent exacerbations NOT just one in the previous year

We recommend that comparison with Mepolizumab is added to the scope and the committee are asked to review their recommendation following comparison with it.

Yours faithfully,

[redacted]

CONFIDENTIAL UNTIL PUBLISHED

Reslizumab for treating asthma with elevated blood eosinophils inadequately controlled by inhaled corticosteroids: ERG critique of the company's updated analyses

Confidential appendix to Evidence Review Group report

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	27th April 2017

This appendix contains commercial in confidence information which is highlighted in blue and underlined

1. Introduction

The second NICE Appraisal Committee Meeting (ACM) for the resilizumab Single Technology Appraisal was held on 11th April. In response to the evidence discussed at the ACM, the NICE Appraisal Committee issued a 2nd Appraisal Consultation Document (ACD). The company (Teva Pharmaceuticals) has provided their response to the 2nd ACD.

In this report we provide an independent critique of the additional analyses submitted by the company.

The company's revised base case is shown in Table 1. This has the following differences from the previous company base case:

- no adjustment of exacerbation rates for the best supportive care arm, so as to reflect the rates observed in clinical practice in the UK;
- changes to the utility values for severe exacerbations;
- vial-based dosing including both 100-mg and 25-mg vials; and
- a new Patient Access Scheme (PAS) with a simple discount for the cost of resilizumab of [redacted].

The changes made by the company are discussed further in the following sections.

Table 1 Revised company base case for adults with severe eosinophilic asthma and 3 exacerbations in the previous year

	Total costs			Total QALYs			ICER
Scenario	**Reslizumab**	**BSC**	**Incremental**	**Reslizumab**	**BSC**	**Incremental**	
ACD1 Base case	[redacted]	£83,417	[redacted]	15.08	11.99	3.09	£25,408
Revised base case	[redacted]	£61,713	[redacted]	15.84	13.64	2.20	£29,870

2. ERG's checks and critique of the company's analyses

The ERG has checked the results produced by the company by running the company's economic model and is able to replicate the results the results shown in Table 1 by making the changes described by the company.

2.1 Exacerbation rate

The company's revised base case uses transition probabilities for resilizumab and best supportive care estimated based on patients who had experienced 3 or more exacerbations in the year previous year. Their analysis makes no adjustment to the exacerbation rates for best supportive care, so as to reflect 'real world' exacerbation rates observed in clinical practice in the UK.

The changes made by the company for exacerbation rates for best supportive care are consistent with NICE committee's preferred approach for the exacerbation rate for best supportive care.

2.2 Utility values for severe exacerbations

The company provided data from studies 3082 and 3083 on the duration of severe exacerbations in patients who had severe eosinophilic asthma and 3 or more exacerbations in the previous year. The mean length of a severe exacerbation for patients receiving resilizumab was [redacted] days, compared to [redacted] days for patients on placebo. A severe exacerbation was defined as an exacerbation 'requiring the use of (additional) systemic steroids'.

The ERG notes the following potential limitations to these exacerbation duration data:

- These data are subject to the same limitations as other outcomes from studies 3082 and 3083, i.e. they may not be reflective of the responses of patients who have lower eosinophil counts and a need for oral corticosteroids (section 4.4 in the 2nd ACD).
- The statistical comparison of severe exacerbation durations was post-hoc (i.e. testing a hypothesis suggested by the data), which may result in false positives; however, this does not influence the company's calculation of utilities.
- The data on severe exacerbation durations are new (not available in the company's submission or clinical study reports), so the ERG could not check them.
- The ERG was unable to find any comparable data on severe exacerbation durations experienced in clinical practice against which to compare the company's data. The effect of reslizumab in reducing the duration of severe exacerbations is clinically plausible, but there is uncertainty as to how closely the company's data would match 'real world' severe exacerbation durations and the variability associated with them.

In the company's original analysis a single utility value was used for both resilizumab and best supportive care and this was applied to the duration of the full model cycle (4 weeks).

The company's new analysis provides specific utility values for each comparator and these have been weighted according the duration of the severe exacerbations (as given above), to account for the fact that severe exacerbations do not last for the full model cycle. The overall mean utility for severe exacerbation in each model cycle is calculated from the weighted utility for the time with severe exacerbation plus the weighted utility for the exacerbation-free ('uncontrolled' utility) remainder time of the model cycle. The ERG considers the calculation used to derive the new utility values for severe exacerbation to be appropriate.

The recalculated severe exacerbation values were 0.54 for patients receiving resilizumab and 0.50 for patients receiving best supportive care, compared to the previously used utility value for severe exacerbation of 0.51 for all patients.

As stated in the ERG report, the utility value estimates for severe exacerbations are somewhat uncertain due to the lack of robust health-related quality of life data. However, the ERG considers the changes the company has made regarding utility values for severe exacerbation in the company's response to the 2nd ACD are reasonable, given the limited availability of evidence. The ERG notes that changing the utility values in this way reduces the ICER by about £1000.

2.3 Dosing

The NICE committee concluded in the 2nd ACD that 'the 25-mg vial could be considered and that any positive recommendation would only be made based on the availability of this size of vial'. The company therefore proposed that vial-based dosing is appropriate, using a combination of 25-mg and 100-mg vials according to dosing based on patients' weight, to minimise wastage. This differs from the previous company analyses that used only 25-mg vials or only 100-mg vials. The ERG considers that if 25-mg vials are made available (and are acceptable to clinicians), then use of these in vial-based dosing would be reasonable.

2.4 Revised Patient Access Scheme

The company has submitted a revised PAS which reduces the acquisition costs of resilizumab from the previous PAS discount of [redacted] to the revised PAS of [redacted]. The revised PAS price for a 25-mg vial of resilizumab is [redacted] compared to the list price of [redacted].

2.5 Effects of individual amendments

The company has provided a breakdown of the effect of each of the amendments on the ICER and is shown in Table 2 (reproduced from company's ACD response Table 1).

Table 2 Summary of ICERs with each implemented amendment

Scenario	ICER
Base case submitted in response to ACD1	**£25,408**
• No adjustment on exacerbation rate	£43,064
• Revised utilities for severe exacerbation, no adjustment on exacerbation rate	£42,025
• Vial-based dosing, no adjustment on exacerbation rate	[redacted]
• Revised PAS, no adjustment on exacerbation rate	[redacted]
Revised base case with all amendments	**£29,870**

3. Summary

The ERG has reviewed the updated analyses made by the company in response to the 2nd ACD. We have checked the analyses and replicated the results. We consider that the company's amendments and their results presented are reasonable, given the limitations of the available data.