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30 November 2012

Dear Mr Boysen

**Re: Omalizumab for the treatment of severe persistent allergic asthma in children aged 6 and over and adults (review of TA133 and TA201)**

Thank you for your email dated 2nd November 2012 inviting comments on the Appraisal Consultation Document (ACD) and Evaluation Report for the above appraisal.

Novartis is extremely disappointed and surprised that this draft guidance from NICE does not recommend omalizumab, thus effectively proposing to reverse the positive TA 133 recommendation for patients aged 12 years and older that was issued in November 2007. We are concerned that, should NICE's draft recommendation become final guidance, patients of all ages with severe persistent allergic asthma will be left without access to this unique and highly innovative treatment option.

We are pleased that the Appraisal Committee has again recognised that omalizumab is a clinically effective treatment for patients with severe persistent allergic asthma. In this respect, the ACD acknowledges the benefits of omalizumab on outcome measures that are relevant to patients with this condition e.g. reductions in asthma exacerbations, reductions in unscheduled use of healthcare resources (e.g. hospitalisations), improvements in health related quality of life (HRQoL) and reductions in exposure to oral corticosteroids (OCS). Such benefits closely align with the scope of the recently announced NHS Mandate which includes national indicators on HRQoL and unplanned hospitalisation in people with long-term conditions, the latter specifically in people under 19 with asthma.

We disagree with the Appraisal Committee's view that omalizumab is not a cost-effective use of NHS resources and believe there are potentially important benefits of omalizumab treatment that have not been fully captured in the independent economic evaluation and subsequent 'additional analyses' conducted by the Assessment Group. We strongly believe that omalizumab can be used cost-effectively when it is appropriately targeted towards subgroups of patients with 'very severe' allergic asthma who are at the highest risk of asthma-related mortality and serious OCS-related side effects.

We are concerned by the lack of clarity in the ACD on four main points:-

1. **<u>Rationale for Proposing to Reverse the TA 133 Recommendation</u>**

   The ACD offers no clear justification for the proposal to reverse the TA 133 recommendation. The ACD should specify the exact changes to the evidence base that led the committee to consider that plausible cost-effectiveness estimates were, in their opinion, higher (i.e. worse) than in 2007. Having discussed this issue with representatives of NICE, we understand the Committee's negative decision to be primarily based on cost-effectiveness grounds due to new evidence on asthma-related mortality (de Vries et al. 2010) that was published since TA 133. If this is the case, this position should be clearly stated in the ACD. Without this justification, stakeholders are left unclear on what specifically led NICE to arrive at their draft decision.

   For future reviews of existing guidance we suggest that NICE includes a dedicated section in the main body of the ACD and the summary table that addresses (i) changes to the evidence base since the previous review (ii) the impact of these changes on the 'most plausible' incremental cost-effectiveness ratio (ICER) and (iii) the rationale for changing the recommendation (if it is different from the recommendation of the previous review). We also suggest that NICE takes steps to ensure that the content of its press releases is completely congruent with the content of its guidance documents. For example, in this case, NICE's press release stated that omalizumab *"was not as clinically effective as was first thought"*. This is not a view stated in the ACD and created considerable confusion for stakeholders regarding the rationale for the draft decision.

2. **<u>Patient Population</u>**

   The ACD focuses mainly on three subgroups of patients receiving maintenance OCS but does not appear to arrive at a clear determination on which one is the most appropriate in UK clinical practice. Based on the ACD content and clinical expert opinion in Evaluation Report we strongly believe that the 3rd population defined on p50 of the ACD **i.e. patients on maintenance OCS <u>or</u> >=4 courses of OCS per year)** is the most clinically relevant population in UK practice and offers the most sound basis for positive guidance to the NHS. Hereafter, we refer to this patient population as ***"Subgroup 3".***

3. **<u>'Most Plausible' ICERs and 'Most Plausible' Asthma-Related Mortality Rate</u>**

   The ACD is vague on what the Committee considers to be the 'most plausible' ICER and cites a wide range of £31K per QALY (based on Watson et al. 2007 asthma mortality rates +15%) to £42K per QALY (based on de Vries et al. asthma mortality rates + 15%). However, it also states that *"The Committee agreed that the asthma-related mortality rates applicable to this appraisal were likely to be between the Watson et al. and De Vries et al. estimates"* (ACD 4.4.9, p47). In principle, we are pleased the Committee agrees that patients in 'very severe' subgroups are at an elevated risk of asthma-related mortality which exceeds the rate reported by de Vries et al. (2010). However, whilst we accept that there is inherent uncertainty, we suggest that the Committee should reach a judgement on where the asthma mortality rate is most likely to fall within this range,

and hence where the 'most plausible' ICER is most likely to fall in the £31K-£42K per QALY range.

The ACD also indicates that the 2.2% proportion of children in the Assessment Group's weighted average cost-effectiveness analyses may be an underestimate. However, employing alternative proportions of children in the Assessment Group model has little impact on the 'overall' age-weighted ICERs.

**4. <u>Rationale for Lack of Consideration of 'Additional' OCS Side-Effects and HRQoL Benefits</u>**

There is strong qualitative evidence highlighted in the ACD and Evaluation Report that chronic treatment with OCS increases the risk of a number of serious adverse effects which are not currently accounted for in the economic modelling due to a paucity of empirical data. The ACD also notes that frequent OCS courses are likely to adversely impact patients' lives but this impact is also not quantified in the OCS-sparing analyses. In a similar vein, we also note that '*The Committee agreed that there could be additional health-related benefits conferred to carers as a result of omalizumab use but that these were currently not quantifiable*' (ACD 4.4.7, p45). On each of these points, we question whether having no empirical evidence despite likely benefit is reasonable grounds for assuming no benefit at all. By not capturing these benefits, we believe that the £31K-£42K per QALY range cited in the ACD underestimates the cost-effectiveness of omalizumab.

These and other issues are discussed in detail in our response which is structured as follows:-

A. *Main Comments on the ACD*
B. *Supplementary/Minor Comments on the ACD*
C. *Comments on the Evaluation Report*
D. *References*

In summary, we accept that there is some uncertainty regarding asthma-related mortality rates in the economic model but feel that, with a mortality rate that is plausible in patients with 'very severe' asthma, this uncertainty could be offset by the unquantifiable benefits of omalizumab on the reduction of 'additional' OCS side-effects and the improvement of carer quality of life. We acknowledge, however, that empirical data are limited in these areas and that this represents a challenge for the Appraisal Committee. Therefore, as you are aware, and to attempt to fully address any remaining empirical uncertainty around the cost-effectiveness of omalizumab, Novartis has submitted a confidential simple discount Patient Access Scheme (PAS) for consideration by the Department of Health and NICE's Patient Access Scheme Liaison Unit (PASLU). A formal submission of the PAS to NICE will follow in due course, subject to ministerial approval. We believe it is important (assuming approval from the relevant bodies mentioned above), that this PAS is considered alongside our comments on the ACD at the next Appraisal Committee meeting on 22nd January 2013.

Also provided with this ACD response is a document entitled ***'Additional Cost-Effectiveness Analyses'***. Further to the agreement obtained from NICE, this document provides some scenario analysis based on the issues raised in points 2 and 3 of this letter. It also provides estimated ICERs with and without the proposed PAS. Please note that this ACD response should only be read in conjunction with the document entitled ***'Additional Cost-Effectiveness Analyses'*** and should not be considered in isolation.

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

Yours sincerely

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## A. Main Comments on the ACD

### 1. Rationale for Proposing to Reverse the TA 133 Recommendation

The ACD offers no clear justification for the proposal to reverse the TA 133 recommendation. The ACD should specify the exact changes to the evidence base that led the committee to consider that plausible cost-effectiveness estimates were, in their opinion, higher (i.e. worse) than in 2007. Having discussed this issue with representatives of NICE, we understand the Committee's negative decision to be primarily based on cost-effectiveness grounds due to new evidence on asthma-related mortality (de Vries et al. 2010) that was published since TA 133. If this is the case, this position should be clearly stated in the ACD. Without this justification, stakeholders are left unclear on what specifically led NICE to arrive at their draft decision.

For future reviews of existing guidance we suggest that NICE includes a dedicated section in the main body of the ACD and the summary table that addresses (i) changes to the evidence base since the previous review (ii) the impact of these changes on the 'most plausible' incremental cost-effectiveness ratio (ICER) and (iii) the rationale for changing the recommendation (if it is different from the recommendation of the previous review). We also suggest that NICE takes steps to ensure that the content of its press releases is completely congruent with the content of its guidance documents. For example, in this case, NICE's press release stated that omalizumab *"was not as clinically effective as was first thought"*. This is not a view stated in the ACD and created considerable confusion for stakeholders regarding the rationale for the draft decision.

### 2. Patient Population

The ACD appears to mainly focus on the three subgroups that were the basis of the additional analyses requested by the Appraisal Committee in July 2012 and conducted by the Assessment Group in August 2012 (ACD 4.4.5, p50; Evaluation Report p611-629). These subgroups include patients who are:-

- **Subgroup 1**: On maintenance oral corticosteroids (OCS) and who were hospitalised in the year before treatment
- **Subgroup 2**: On maintenance OCS but who have not necessarily been hospitalised in the year before treatment
- **Subgroup 3**: On maintenance or frequent courses of OCS (for example, 4 or more courses per year) but who have not necessarily been hospitalised in the year before treatment.

We agree with the discussion in the ACD on the relevance of these subgroups to UK clinical practice, for example:-

- *"The Committee accepted that there are limitations to using previous hospitalisation as a sole criterion for determining clinical need for omalizumab."* (ACD, 4.4.4, p42-3) **[i.e.**

**there are limitations to defining clinical need based on the Subgroup 1 definition]**

- *"The Committee noted that the clinical specialists preferred an alternative way of a identifying candidates for treatment with omalizumab, that is people with asthma at step 5 of the 'British guideline on the management of asthma' (BTS/SIGN) with poorly controlled asthma who are treated with continuous or multiple courses of oral corticosteroids per year, irrespective of whether they had recently been admitted to hospital." (ACD, 4.4.4, p42-3)* **[i.e. UK clinical experts prefer to determine clinical need based on the Subgroup 3 definition]**
- *"The clinical specialists explained that they would offer omalizumab not only to people on maintenance oral corticosteroids, but also to some people who required frequent courses of oral corticosteroids… The Committee accepted that there are significant risks associated with oral corticosteroids, and that frequent use may have a considerable impact on the lives of people with severe asthma." (4.4.5, p43-44)* **[i.e. UK clinical experts prefer to determine clinical need based on the Subgroup 3 definition and the Appraisal Committee recognises the adverse impact of OCS on patients treated according to the Subgroup 3 definition]**
- As per point 3 below, the 'most plausible' ICERs are stated in the ACD as £31K-£42K per QALY. Whilst the ICERs are similar between the three subgroups, the above ICERs, as quoted in the ACD, are unique to subgroup 3 **[i.e. this appears to indicate a Appraisal Committee preference for subgroup 3]**

Based on these points and the linked content in the Evaluation Report, we do not believe that there is a sound clinical rationale for targeting omalizumab to subgroup 1 (or reverting to the very similar TA 133 recommendation). Whilst subgroup 2 appears to be more appropriate to UK clinical practice than subgroup 1, based on the ACD content and consistent clinical expert opinion (in the Evaluation Report and Committee meetings to date), we strongly believe that **Subgroup 3 i.e. patients on maintenance OCS <u>or</u> >=4 courses of OCS per year** is the most clinically relevant population in UK practice and offers the most sound basis for positive guidance to the NHS.

## 3. <u>'Most Plausible' ICERs</u>

The ACD is very unclear on what the Committee considers the 'most plausible' ICER. As stated in point 2 above, the 'most plausible' ICERs appear to be based on subgroup 3 and range from £31K per QALY (based on Watson et al. mortality data, inflated by +15% = 1.45% age-weighted rate) to £42K per QALY (based on de Vries et al. mortality rate, inflated by +15% = 0.46% flat rate). However, the ACD also states that these ICERs are based on 'optimistic' assumptions. It is not clear which specific assumptions the Committee considers to be 'optimistic'. The document on p611-629 of the Evaluation Report (*'Additional analyses requested by NICE on behalf of the Committee; 29th August 2012')* describes all of the assumptions implemented in the analyses. In our view, the 'base case assumptions' described in table 2 of this document are appropriate given the underlying natural history of severe asthma and the clinical benefits experienced by patients treated with omalizumab in UK clinical practice.

Based on the ACD, the principal cause of uncertainty around the ICERs appears to be related the choice of asthma related mortality rate, which is discussed in more detail as follows.

## 4. Asthma-Related Mortality Rate

### a. 'Most Plausible' Mortality Rate Estimates for Cost-effectiveness Analysis

This issue has been discussed in detail in our submission, the Assessment Report, our response to the Assessment Report and the first Appraisal Committee meeting on 3rd July 2012. We also note that clinical experts agree that patients with more severe asthma experience more frequent exacerbations and are at higher risk of mortality (Evaluation Report, p624, Expert Responses to Q3).

In principle, we are pleased the Committee agrees that patients in 'very severe' subgroups are at an elevated risk of asthma-related mortality which exceeds the rate reported by de Vries et al. (2010). As we highlighted in our response to the Assessment Report, the mortality rate reported by de Vries et al. applies to a broad maintenance OCS (i.e. BTS/SIGN step 5) population derived from a primary care database and, as such, the mortality rate is likely to be lower than one might expected in a high-risk patient population eligible for treatment with omalizumab.

The thorough systematic reviews conducted by Novartis and the Assessment Group ensure that the Committee has the best currently availably evidence (Watson et al. and de Vries et al.) to inform judgments about the plausible rates of asthma mortality in the patients with 'very severe' allergic asthma. However, we note that the ACD is vague on the specific rate that the Committee considers to be plausible in such patients, for example:-

- *"The Committee agreed that the asthma-related mortality rates applicable to this appraisal were likely to be between the Watson et al. and De Vries et al. estimates." (ACD, 4.4.9, p46-47)*

Whilst we accept that there is inherent uncertainty, we suggest that the Committee should reach a judgment on where the asthma mortality rate is most likely to fall within this range, and hence where the 'most plausible' ICER is most likely to fall in the £31K-£42K per QALY range.

Whilst asthma-related mortality has been discussed at length in this appraisal, it was not discussed in detail in Part 1 of the second Committee meeting held on 3rd October 2012. Therefore, the full extent of the Committee's remaining concerns on this issue was not apparent to representatives of Novartis or other attendees at the meeting. Given that the appraisal process was delayed for three months for the Assessment Group to conduct additional analyses, there seems to have been a missed opportunity to estimate cost-effectiveness based on alternative values in between those reported by Watson et al. and de Vries et al in order to avoid the presentation of such a wide ICER range. We have explored this issue further in the separate document entitled '***Additional Cost-Effectiveness Analyses***' and hope that this analysis is helpful for the Committee.

**b. ‘<u>Expected Number of Deaths in Omalizumab Clinical Trials Based on Watson et al. Rates</u>**

We note the following statement in the ACD:-

- *“The Assessment Group also highlighted that, if the asthma-related mortality rate used by the manufacturer (2.478% in adults aged 45 years and over derived from Watson et al.) was applied to the INNOVATE study, 2 or 3 asthma deaths would have been expected out of the 100 observed clinically significant severe exacerbations, and, if applied to the APEX study, 6–7 deaths from asthma would have been expected among the 261 observed clinically significant severe exacerbations. However, because nobody in these trials died from asthma, the Assessment Group commented that the rates for asthma-related mortality used in the manufacturer’s submission for adults and adolescents were likely to have overestimated mortality”* (ACD 4.2.15, p29-30).

Our comment on this point may be academic given that, as noted in the previous section, the *“The Committee agreed that the asthma-related mortality rates applicable to this appraisal were likely to be between the Watson et al. and De Vries et al. estimates.” (ACD, 4.4.9, p47).* However, the majority of this comment relates to a factual inaccuracy, based on a misinterpretation of the data, which needs to be addressed.

The observation that applying the Watson et al. rate of (2.478% mortality) to the 100 clinically significant severe exacerbations observed in the standard therapy arm results in 2 or 3 asthma deaths is theoretically correct. If one employs a weighted average calculation of mortality +15% as employed in the most recent Assessment Group model (dated 27 Sep 2012), the weighted average rate of 1.45% indicates that 1 asthma death may be expected in the standard therapy arm. As previously indicated during this appraisal, in omalizumab clinical trials the standard of care patients received far exceeded the care patients routinely receive in UK clinical practice e.g. therapy was rigorously optimised and patients had face-to-face contact with a doctor and/or nurse every 2 to 4 weeks depending on the frequency of dosing. In this highly atypical, carefully managed setting it is perhaps not surprising that no asthma fatalities occurred.

However, the calculation of likely asthma deaths in the APEX study, as described in the ACD is factually inaccurate. APEX was a retrospective ‘before-and-after’ study in which patients were identified by virtue of the fact that they had received treatment with at least one dose of omalizumab in UK clinical practice. The clinical notes of patients identified in this way were then interrogated for one year prior to their initiation on omalizumab and for up to one year after. By definition, all of these patients were alive up to the point they received omalizumab treatment (i.e. none of the exacerbations these individuals experienced in the prior year could have been fatal). The annualised exacerbation rate of 1.73 exacerbations in the year post omalizumab was based on a mean follow up duration of 316 days. This means that an estimated 204 exacerbations were experienced in the period during which study patients were at risk of death *[(316 days/365 days) x 1.73 exacerbations x 136 patients = 204 total exacerbations]*. No data are available from APEX on the CSS:CS split but assuming that 52.4% of exacerbations were CSS exacerbations as per INNOVATE, this means that 204 x 52.4% = 107 CSS exacerbations occurred in the period where an asthma death was possible.

This means that 3 deaths could in theory occur at a mortality rate of 2.478%, or 2 deaths at the weighted average rate of 1.45%. The ACD statement regarding 6-7 deaths being expected in the APEX study should therefore be corrected. It is important to note that all of these patients were closely managed at ten of the top respiratory centres in the UK and had frequent 2 or 4 weekly face-to-face contact with health care professionals, so it is perhaps not surprising that no deaths occurred in the APEX study due the level and quality of care received. We suggest that the ACD also acknowledges this point.

One also needs to be cautious about applying mortality rates to the relatively small sample sizes in omalizumab clinical trials. For example, the only death in the RCTs included in our submission was in the placebo arm of the EXALT study (section 3.9.1, p68 of our submission) and resulted from a severe asthma exacerbation ('status asthmaticus'). As per Appendix C of our submission, there were 51 CSS exacerbations in the standard therapy arm of EXALT. It would arguably be unreasonable to assume an asthma-related mortality rate of 1/51 =1.96% solely on this basis. In this respect, the systematically identified UK-specific asthma mortality data from Watson et al. and de Vries et al. arguably provides a more relevant starting point for debate around asthma related mortality given the very large sample sizes involved.

**5. <u>Proportion of Children in the Weighted Average ICER Calculations</u>**

We note the comments on this point in the ACD:-

- *"The Committee acknowledged that the ICERs for the overall population and for adults and adolescents were similar because children were assumed to represent only a very small proportion of the overall population treated with omalizumab. However, the Committee acknowledged that the lower use of omalizumab in children may reflect the guidance recommendation in NICE technology appraisal 201, and therefore may underestimate the proportion of children who might otherwise be considered for omalizumab treatment."* (ACD 4.4.15, p50-51).

In the additional analyses dated August 2012, the Assessment Group calculated a weighted average ICER using a 2.2% proportion of children and a 97.8% proportion of adults and adolescents aged >=12 years. This 2.2% figure was an estimate, provided by Novartis in our submission, of the proportion of patients receiving omalizumab who were aged 6-11 years. These data were not necessarily intended for the purpose for which they ultimately have been used, but would be a reasonable assumption in a scenario where the negative TA201 recommendation was maintained. If this was a concern of the Committee, we are surprised that it was not discussed in Part I of the meeting on 3 October 2012 where there was an opportunity to obtain clarification on this figure. In an environment with positive NICE guidance in children aged 6-11 years, we agree that the 2.2% figure could be a slight underestimate.

However, deriving alternative proportions of children that are specific to the severe persistent asthma population is challenging. The GPRD-based sizing study we discussed in the *'Impact on the NHS Section'* of our submission (p109-112) attempted to quantify the

number of patients aged 6-11 years. However, the numbers of severe paediatric patients in the GPRD sample could not be quantified due to insufficient patient numbers. In the absence of condition-specific information, the logical alternative is to look to the proportion of the general population in England & Wales who are >=6 years of age and calculate the proportion who are 6-11 years old. Based on mid-2011 census data for England & Wales the proportion of patients who are >=6 years of age and 6-11 years old is 7.3% (Office for National Statistics, 2011). We have tested this value and the mid-point value between 2.2% and 7.3 (i.e. 4.75%) in the cost-effectiveness model provided by the Assessment Group. Our assessment is that the 4.75% figure is more plausible than the 7.3% figure. This is because even if a positive NICE recommendation was issued for children aged 6-11 years, the distribution of patients on therapy will remain skewed towards patients aged >=12 years who have benefited from positive NICE guidance for over 5 years. It is important to note however, that alternative proportions of children in the Assessment Group model have very little impact on the 'overall' age-weighted ICERs (please see the separate documented entitled ***'Additional Cost-Effectiveness Analyses').***

We are not aware of any evidence that this type of 'very severe' allergic asthma is more or less common in young children than in patients aged 12 years and older. Therefore, we feel that the above figures fully address the uncertainty regarding this input parameter.

**6. <u>Inclusion of Full Range of OCS Adverse Events in Cost-effectiveness Model</u>**

We note the following statements in the ACD:-

- *"The Committee noted that the Assessment Group's analysis had taken into account the disutility from several long-term adverse effects including bone fracture, diabetes mellitus, peptic ulcer, myocardial infarction and stroke, cataract and glaucoma, weight gain, non-Hodgkin's lymphoma, adrenal insufficiency and sleep disturbance. However, the Committee concluded that other adverse effects, such as obesity, hypertension, mood changes, depression, psychosis, thinning skin, delayed wound healing, reduced growth in children, and increased risk of infection were additional important factors that had not been captured when calculating the QALY." (ACD 4.4.13, p49)*
- *"The Committee noted that the additional QALYs from unidentified adverse effects of oral corticosteroids would need to be twice or more of those derived from known adverse effects, and was not persuaded that this was a plausible assumption." (4.4.16, p51)*

Firstly, we are surprised that the committee did not feel this was a plausible assumption given that the Clinical Expert who was asked directly about this at the Appraisal Committee meeting on 3 October was in no doubt that it was plausible in their patient population.

Secondly, the analysis conducted by the Assessment Group, based on the Novartis analysis, included OCS side-effects where there was a quantifiable increased risk associated with maintenance OCS. OCS have been in routine clinical use in severe asthma for several decades and, whilst they are known to be associated with a number of serious long-term side effects, high quality published evidence of their adverse effects is extremely limited. The list of additional OCS adverse effects described by the committee (ACD 4.4.13, p49)

approximately doubles the number of adverse effects included in the most complete Assessment Group scenario analysis (ACD 4.4.13, p49). Any number of further adverse effects could be drawn from the list provided on p7 of the Asthma UK submission (Evaluation Report, p503). OCS-related growth impairment in children in particular is likely to be associated with substantial disutility (our submission provided detailed work up of a disutility estimate of 0.061 for this specific adverse effect, see p147-148).

Thirdly, the current analyses are likely to underestimate the HRQoL impact of OCS-sparing effect of omalizumab simply because data are only available to allow quantification of the effect of stopping OCS completely, i.e. reducing the relative risk of OCS adverse effects to zero. An additional unquantified benefit for omalizumab is the impact of reduced adverse effects in patients reducing the dose of maintenance OCS or reducing the number of OCS courses (but not stopping completely). With respect to the latter we note that the Committee accepted the frequent use of OCS may have a significant impact on patients' lives:-

- *"The Committee accepted that there are significant risks associated with oral corticosteroids, and that frequent use may have a considerable impact on the lives of people with severe asthma." (ACD 4.4.5, p43-44).*

What is clear is that there are a considerable number of OCS-related adverse effects that have not been incorporated into the cost-effectiveness model due to lack of good quality evidence and that the benefits for patients reducing their OCS exposure are also not captured. This means that the £31K-£42K per QALY ICER estimate in the ACD is likely to underestimate the cost-effectiveness of omalizumab. We question whether no empirical evidence on additional OCS adverse effects is a reasonable grounds for assuming no additional benefit at all.

## 7. Inclusion of Health-related Quality of Life for Carers

We note the following statements in the ACD:-

- *"The Assessment Group was not aware of any evidence to provide adequate estimates on health-related quality-of-life benefits not currently captured in the economic modelling, for example in carers." (ACD 4.2.32, p41)*
- *"The Committee also heard that the impact on families and carers may include anxiety, sleep deprivation, and emotional and financial pressures."* (ACD 4.4.2, p41-42)
- *"The Committee accepted that severe uncontrolled asthma can severely reduce quality of life among people with the condition, as well as their families and carers."* (ACD 4.4.2, p41-42)
- *"The Committee also agreed that there could be additional health-related benefits conferred to carers as a result of omalizumab use, and that these, if quantifiable, could be included within NICE's reference case." (ACD 4.4.7, p45)*
- *"The Committee considered the benefits to carers provided by omalizumab, which may not have been captured in the QALY calculations for omalizumab as an add-on*

*treatment to standard care. The Committee noted that no empirical and quantifiable evidence relating to potential carer benefits had been included in the manufacturer's submission, and that therefore the Assessment Group did not try to include any carer benefits formally in their additional analyses. The Committee agreed that there could be additional health-related benefits conferred to carers as a result of omalizumab use but that these were currently not quantifiable. The Committee recognised that the approach to estimate utility gain in light of the lack of evidence taken in NICE technology appraisal 246 (Pharmalgen for the treatment of bee and wasp venom allergy) was not appropriate to use here as omalizumab does not provide a cure for asthma." (ACD 4.4.17, p52)*

We accept that there is no empirical evidence of a utility benefit for carers of patients (predominantly young children) who receive treatment with omalizumab. However, as the Committee clearly accepts that there is severely reduced quality of life for carers, we question whether no empirical evidence on carer HRQoL benefit is a reasonable grounds for assuming no benefit at all.

The justification that this approach should be taken because omalizumab is not a 'cure' for asthma is both arbitrary and weak given that the cited example of TA 246 gives no impression that Pharmalgen is a 'cure' for bee and wasp venom allergy. For example:-

- *"The Committee considered that the available evidence base for Pharmalgen was of **poor quality** and was **limited**. On balance, it was persuaded that Pharmalgen had demonstrated **some efficacy** in **reducing the rate and severity** of systemic reactions following a bee or wasp sting. However, the Committee considered that the **relative efficacy could not be quantified with certainty**."* (TA 246, 4.3.7, emphasis added).

**8. Innovation**

The statement that *"The manufacturer's submission did not discuss the innovative nature of omalizmab"* (ACD, 4.3.1) is factually inaccurate and misleading in the context of this appraisal and the two previous technology appraisals (TA 133 & TA 201). The judgement on innovation is one for the Appraisal Committee to make based on the written submissions and verbal testimonies of consultees and commentators. Aside from the fact that our submission did refer to innovation in three places, there is no requirement in a manufacturer MTA submission to specifically discuss the innovative nature of the product in question. That said, our submission clearly portrayed a picture of omalizumab as a medicine that is innovative in its ability to make a significant and substantial impact on health-related benefits.

Numerous statements from NICE, its Appraisal Committees and non-manufacturer stakeholders also attest to the innovative nature of omalizumab:-

- The slides from the last Appraisal Committee meeting on 3 October include reference on slide number 22 to *'Conclusions from previous meeting [on 3 July 2012]'*. The penultimate conclusion is that: ***"Omalizumab is an innovative treatment and a step-change".***

- Representatives of NICE and its Appraisal Committees have also acknowledged that severity of illness, stakeholder input and **significant innovation** were 'special circumstances' that enabled NICE to recommend omalizumab in TA 133 despite a most plausible ICER which, in NICE's opinion, was slightly greater than £30,000 per QALY (Rawlins et al. 2010).
- TA 133 guidance states that *"The Committee heard from patient experts and clinical specialists that omalizumab has resulted in **life-changing improvements in quality of life** for some patients with severe unstable IgE mediated asthma."* (TA133, 4.3, p13).
- The current ACD states the following: *"The Committee heard from patient experts and clinical specialists that omalizumab has resulted in **life-changing improvements in reducing the number of asthma related clinically significant exacerbations."*** (ACD, 4.4.6, p44-45)
- Similarly, in the 'overview' section of the Evaluation Report *"It is clear {from people living with severe asthma] that it has brought **life changing benefits to the small number of people for whom omalizumab is suitable** and in whom other treatment options have been exhausted."* (Evaluation Report, p36).
- Also in the 'overview' section, *"Consultees agreed that **omalizumab has been the only significant advance in the management of severe asthma in the past 30 years."*** (Evaluation Report, p30).

No evidence has been presented during the course of the present appraisal that shows omalizumab to be any less innovative than it was at the time of the last review. Omalizumab remains the first and only anti-IgE therapy for patients with severe allergic asthma. Rather than non-specifically targeting allergic and/or inflammatory processes like pre-existing asthma therapies, omalizumab specifically targets IgE, a key mediator of allergic reactions. Despite being launched in the UK in 2005, no direct alternatives to omalizumab have since become available and none are expected to be available for at least the next few years.

The ACD wording should be changed to ensure that the highly innovative nature of omalizumab is clearly reflected. This comment also applies to the innovation entry in the 'Summary of Key Conclusions' section on p53.

## 9. NICE Approval of Medicines with ICERs of >£30,000 per QALY

As stated above, representatives of NICE and its Appraisal Committees have also acknowledged that severity of illness, stakeholder input and significant innovation were 'special circumstances' that enabled NICE to recommend omalizumab in TA 133 despite a most plausible ICER which, in NICE's opinion, was slightly greater than £30,000 per QALY (Rawlins et al. 2010).

We also note the following information in the NICE Guide to the Methods of Technology Appraisal (NICE 2008):-

6.2.23 *Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the technology as an effective use of NHS resources will specifically take account of the following factors.*

- *The degree of certainty around the ICER. In particular, the Committee will be more cautious about recommending a technology when they are less certain about the ICERs presented.*
- *Whether there are strong reasons to indicate that the assessment of the change in HRQL has been inadequately captured, and may therefore misrepresent the health utility gained.*
- *The innovative nature of the technology, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the QALY measure.*

*6.2.24 As the ICER of an intervention increases in the £20,000 to £30,000 range, the Committee's judgement about the acceptability of the technology as an effective use of NHS resources will make explicit reference to the relevant factors listed above.*

*6.2.25 Above a most plausible ICER of £30,000 per QALY gained, the Committee will need to identify an increasingly stronger case for supporting the technology as an effective use of NHS resources, with regard to the factors listed above.*

Whilst the Methods Guide wording has changed slightly since the 2004 version which was in place at the time of TA 133, the ACD includes no clear reference to the reasons for the provisional decision (i.e. revoking previously positive guidance) in light of the above clauses. This is an important consideration, as the ACD and Evaluation Report indicate that omalizumab has strong grounds on the 2nd and 3rd bullet points of section 6.2.23 of the Methods Guide as cited above.

## B. Supplementary/Minor Comments on the ACD

| Page | Section | Comment |
|---|---|---|
| 8 | 4.1.5 *"The primary outcomes for INNOVATE were the rate of clinically significant asthma exacerbations, the rate of clinically significant severe exacerbations and the rate of emergency visits for asthma."* | This lists three outcome measures as primary outcome measures. Only the first one in the list was the primary outcome measure. |
| 9 | 4.1.6 *"The Assessment Group therefore did not pool the data from EXALT and IA-04 with the INNOVATE trial for the base-case analysis, but only for sensitivity analysis in the economic evaluation."* | This sentence is unclear and requires rewording. Only EXALT and INNOVATE were included in the exploratory pooling. |
| 12 | 4.1.11 *"The relative risk of total exacerbations in the population taking maintenance oral corticosteroids was 0.293 (compared with 0.74 in the total population)…"* | The relative risk should be 0.662 not 0.293. This comment was made on the Assessment Report in June 2012 and was accepted as a correction by the Assessment Group. |
| 17 | 4.1.18 *"74% of people randomised to omalizumab experienced a 0.5-point or greater increase compared with 26% with the comparator, p<0.001)"* | This should read as "61% of people randomised to omalizumab experienced a 0.5-point or greater increase compared with 48% with the comparator, p=0.008)" |
| 20 | 4.1.23 *"The Assessment Group commented that, because of significant design flaws in the studies, the evidence for a clinically significant oral corticosteroid sparing effect of omalizumab was potentially biased."* | Many of the studies in question were observational studies purposely designed to answer questions of clinical-effectiveness in real world settings. It is not a significant design flaw if the study was specifically designed to measure important clinical and patient reported outcomes in a 'real world' setting.<br><br>Whilst potential bias is more of an issue in observational study designs, it is important to note the substantial and relatively consistent proportions of patients that stopped OCS or reduced their OCS dose in all studies. |
| 28 | 4.2.12 *"In contrast, in the EXALT study, the asthma had responded adequately to omalizumab at 16 weeks in 8.6% of* | This statement needs rewording for accuracy. We suggest "In contrast, in the EXALT study, 8.6% of patients who |

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| | *people, but the response was no longer adequate at 32 weeks."* | had responded to omalizumab at 16 weeks were no longer responders at 32 weeks" |
| 28 | 4.2.11, Penultimate line | Missing bracket "… using data from EXALT)." |
| 28 & 47 | 4.2.13, *"The Assessment Group commented that, to estimate the health related quality-of-life benefit with omalizumab, measuring EQ-5D directly is more appropriate than the manufacturer's method of mapping Asthma Quality of Life Questionnaire scores (from INNOVATE) onto EQ-5D values. In addition, the manufacturer assumed that children under 12 years do not experience any improvement in health-related quality of life with omalizumab until they reach 12 years whereas the Assessment Group considered that the observational study of children by Brodlie suggested that young children also experience an improvement in asthma-related quality of life."; and*<br><br>4.4.10 *"The Committee concluded that the evidence presented by a patient expert, and the results from an observation study in children, showed that the utility values used in the manufacturer's economic model did not adequately capture the potential health related quality-of-life benefits of omalizumab for children. The Committee therefore preferred the Assessment Group's approach in which the same utility gain was assumed for adults, adolescents and children."* | We are pleased that the Committee accepted the Assessment Group's pragmatic assumption and note the supporting evidence from the observational study Brodlie et al. which was unpublished and not available to Novartis at the time of our submission. |
| 29 | *4.2.15 "…and when clinicians, in a stepwise approach to treatment, are likely to offer patients omalizumab".* | We disagree, our submission offered a thorough discussion on the place of omalizumab in therapy and provided extensive subgroup analysis in various positions in the treatment pathway. |

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| 30 | 4.2.15 – Line 11 | Typo "ICERS" should read "ICERs" |
| 30 | 4.2.15 *"The Assessment Group commented that there is uncertainty about the association between clinically significant severe exacerbations and death. The Assessment Group considered that, because of this, the manufacturer may have excluded relevant studies from its systematic review on asthma related mortality."* | We disagree. The second sentence does not logically follow this first. We agree that there is uncertainty about the association between clinically significant exacerbations and death. However, our systematic review attempted to identify all possible definitions of 'severe' exacerbations and systematically located all available evidence that linked these event definitions to rates of asthma-specific death. The only studies that would have been excluded were those that could not link severe exacerbation events to asthma deaths i.e. those that were outside the scope of the systematic review. Whilst studies like de Vries et al. were excluded, they were excluded because they did not meet the criteria for the review (and hence did not fit with the structure of our model). |
| 31 | 4.2.17 *"…19.8% of the INNOVATE trial at baseline".* | This is incorrect. Should read 21.7% (calculated as 91/419). |
| 32 & 47 | 4.2.19 *"However, to estimate health-related quality of life for day-to-day symptoms, the Assessment Group used EQ-5D data from EXALT, whereas the manufacturer mapped Asthma Quality of Life Questionnaire scores from INNOVATE onto EQ-5D values."; and*<br><br>4.4.10 *"Secondly, the Committee was aware that the manufacturer and the Assessment Group used different methods of estimating health-related quality of life for day-to-day asthma symptoms. The Committee noted that the Assessment Group's approach, using EQ-5D values directly collected in the EXALT trial, resulted in a lower quality-of-life benefit for people whose asthma responded to omalizumab than did the manufacturer's approach of mapping Asthma Quality of Life Questionnaire scores collected in the INNOVATE trial* | This approach is not unreasonable. However, as stated in the first Appraisal Committee meeting on 3 July, the choice of utility data is of limited relevance in this appraisal as the magnitude of utility differences between treatment arms are almost identical in the subgroup analyses that are the primary focus of this review. We suggest that the ACD acknowledges that the differences are minimal. |

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| | *onto EQ-5D values. The Committee preferred the direct estimates of EQ-5D, in line with the NICE reference case."* | |
| 34 | 4.2.20 *"… and 15 minutes of nurse's time at £47/hour to monitor the patient for the first 3 times a patient received omalizumab. From the fourth administration up to the 16-week assessment, monitoring by the specialist nurse was assumed to take 1 hour."* | This in not correct. As per our submission (section 4.5.2, p93), we assumed monitoring of patients for 2 hours following the first 3 administrations of omalizumab and for 1 hour following the additional administrations up to and including the 16 week responder assessment. On this basis, patients on q4wk dosing would requires 8 hours of monitoring and patients on q2wk dosing would require 12 hours of monitoring. We have assumed that this periodic monitoring would physically only take up to 15 minutes per hour as, in practice, the specialist nurse administering omalizumab would generally ask the patient to sit in the waiting room and periodically check on them (e.g. for injection site reactions, general wellbeing, vital signs and blood pressure as appropriate). |
| *36* | 4.2.24 *"health losses expressed in DALYs are equivalent to health <u>losses</u> expressed in QALYs.* | We think this should probably say "… health <u>gains</u> expressed in QALYs" as patients were assumed to gain utility when they stopped OCS (the level of gain being equivalent to the utility loss associated with OCS use). |
| 37 | 4.2.25 *"Incorporating the adverse effects of oral corticosteroids in the maintenance oral corticosteroids subgroup reduced the ICER for omalizumab as an add-on treatment to standard care compared with standard care alone from £50,181 to £33,786."* | The £33,786 figure is incorrect. This is based on the ICER in the original Assessment Report but the Assessment Group subsequently issued an erratum on the ICERs incorporating OCS adverse effects. The erratum was sent to us by NICE on 6th July 2012 – based on this document, the correct ICER is £44,292. |
| 38 | 4.2.27 *"These analyses model alternative assumptions on…. carer benefits".* | No analysis was conducted by the Assessment Group on carer benefits. |
| 42 | 4.4.3 *"One clinical specialist noted that* | We fully agree with the Committee's |

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| | *the number of people currently being offered omalizumab in his practice accounts for approximately 1 in 200 people with asthma and approximately 8 in 200 people with asthma are at step 5 of the 'British guideline on the management of asthma'. The Committee concluded that only people with the most severe persistent allergic asthma despite optimised treatment would currently be offered omalizumab. The Committee concluded that only people with the most severe persistent allergic asthma despite optimised treatment would currently be offered omalizumab."* | conclusion. However, the 1 in 200 and 8 in 200 estimates may be slight overestimates. For example, as per the de Vries et al. (2010) study, 3.48% of asthma patients are treated at BTS/SIGN step 5. If 8 in 200 patients (4%) were offered omalizumab, approximately 0.14% of all patients at step 5 would be offered omalizumab. As per the comments in our response to the Assessment Report, based on estimated omalizumab patient numbers at the end of 2011, we estimated the proportion of patients receiving omalizumab at step 5 to be 0.03%. Even accounting for offering omalizumab to a proportion of patients who do not respond, the proportion being offered omalizumab is unlikely to be higher than 0.05%. On this basis it is unlikely that more than 3 patients in 200 at step 5 were being offered omalizumab at the time of our submission. |
| 58 | Section 7 *"NICE proposes that the guidance on this technology is considered for review by the Guidance Executive in March 2016"* | Omalizumab is an established medicine that has been available for more than 7 years. We expect relatively minimal change to evidence base for omalizumab in the EU licence population over the coming years and suggest that NICE considers a longer review cycle. |

## C. Comments on the Evaluation Report

Thank you for sharing the comprehensive evaluation report. We have three main comments to make on this document.

### 1. *Assessment Group Responses to Novartis Comments on the Assessment Report*

We note that the Assessment Report comprises a large proportion of the Evaluation Report (p67-421). We also see on p467-491 that the Assessment Group has provided detailed responses to our June 2012 comments on the Assessment Report and thank them for making the stated amendments to their final report. The only response that is unclear is the one in the final row of the table on p489 which responds to our view that rates rather than probabilities should have been used on the asthma death worksheet of the economic model:-

- *"We acknowledge the error and accept the correction. However, it should be noted that, even for Scenario 4, the impact on the cost-effectiveness results is minor. The reduction in ICER from using the revised model in Scenario 4 is between £1,058 (hospitalization population paediatric) and £2,477 (overall population paediatric)."* (Evaluation Report, p489)

Based on this statement, the correction is accepted. However, correspondence from the Assessment Group forwarded to us by NICE on 27th September 2012 indicates that the Assessment Group did not consider the correction to be necessary. This is consistent with the most recent version of the Assessment Group model in which probabilities are used in the 'Asthma Death' worksheet rather than rates as we suggested. The impact of implementing rates may be minor but it does have a positive impact on the ICER, particularly in scenarios with higher asthma mortality rates. Whilst the ACD states that some of the assumptions in the cost-effectiveness assessment are considered 'optimistic', it should be noted that there are some like this one that are more 'pessimistic' in nature.

### 2. *Implementation of Exacerbation Rates in Latest Assessment Group Analyses*

The document on p611-629 entitled *'Additional analyses requested by NICE on behalf of the Committee; 29th August 2012'* indicates the following in Table 3 (The Committee's base-case assumptions and alternative scenarios):-

- '***Baseline rate of exacerbations***' - *'Corresponding subgroup data from APEX for both children and adults and adolescents. The percentage split between CSNS and CSS exacerbations observed in INNOVATE is used to estimate the split in total CS exacerbations in APEX.'*
- ***'Omalizumab effect on exacerbations'*** – *'Corresponding subgroup data from INNOVATE for both children and adults and adolescents'.*

One issue that we did not identify in our initial factual accuracy check, but which has become apparent on more detailed inspection of the additional analyses, is that the data inputs in the Assessment Group model do not fully reflect these assumptions. For baseline

event rates and omalizumab treatment effect, the data for Clinical Significant Non-Severe (CSNS) exacerbations (adults and adolescents) have been applied to children aged 6-11 years but the data for Clinically Significant Severe (CSS) exacerbations have not. Instead, the CSNS exacerbation data is employed for CSS exacerbations. If the intention was to have the same exacerbation data for adults, adolescents and children as the 'Additional Analyses' document suggests, the result is that the effect of omalizumab on CSS exacerbations in children aged 6-11 years is being underestimated. To correct this, the following changes would need to be made in the 'Parameters' worksheet of the model:-

- C60 & C64 - change formula from '**=a_st_CSNS**' to '**=a_st_CSS'.**
- C80 & C84 – change formula from '**=a_rr_CSNS**' to '**=a_rr_CSS'.**
- C101 & C105 – change formula from '**=a_rr_CSNSall**' to '**=a_rr_CSSall'.**

The impact of making this change on the ICERs in children aged 6-11 years is significant. For example, in the latest model version entitled "Copy of Omalizumab subgroup 1 base-case.xlsm", dated 27th September 2012:-

- The ICER for children aged 6-11 years in Subgroup 3 reduces from £60,852 to **£48,732**
- The age-weighted overall ICER in Subgroup 3 reduces from £31,159 to **£30,927** (although this impact is small, when modelling higher proportions of children aged 6-11 years as per point A5 of this response, the impact of the lower paediatric ICER becomes more relevant)

## 3. The Overview

Regarding the section entitled *'The Overview'* (dated June 2012) on pages 6-64 of the Evaluation Report, we note that this document summarises evidence from stakeholder submissions and the Assessment Report. We also note that it does not take into account any comments raised by stakeholders on the Assessment Report, the discussions at the Appraisal Committee meetings in July and October 2012 or the additional analyses carried out by the Assessment Group in August. As a consequence, this section does contain some factual inaccuracies and misinterpretations that we have already had the opportunity to comment on during the Appraisal process. Furthermore, as the ACD is a more up to date summary than *'The Overview'*, we have focused our comments on the ACD rather than re-iterating comments that we have already put forward, many of which have already been considered and addressed.

## D. References


- **de Vries F, Setakis E, Zhang B, van Staa TP (2010).** Long-acting beta2-agonists in adult asthma and the pattern of risk of death and severe asthma outcomes: a study using the GPRD. *Eur Respir J*; **36**: 494-502.
- **NICE (2008).** Updated guide to the methods of technology appraisal - June 2008. http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/?domedia=1&mid=B52851A3-19B9-E0B5-D48284D172BD8459 (last accessed 26th November 2012).
- **Office for National Statistics (2011).** Mid-2011 Population Estimates: England and Wales; estimated resident population by single year of age and sex. http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-262039 (last accessed 26th November 2012).
- **Rawlins M, Barnett D, Stevens (2010).** Pharmacoeconomics: NICE's approach to decision-making. *Br J Clin Pharmacol*; **70**(3): 346-9.
- **Watson L, Turk F, James P, et al. (2007)** Factors associated with mortality after an asthma admission: a national United Kingdom database analysis. *Respir Med*; **101**: 1659-64.