Response to Novartis Response and Factual Inaccuracies

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Main Comments on the Assessment Report : Clinical Effectiveness: Efficacy			
5	A) Long term efficacy of omalizumab	We note the statements in the Assessment Report regarding long-term efficacy:- • *"There was a lack of any randomised evidence relating to long-term efficacy and only very limited evidence from observational studies was identified."* (Executive Summary p25 & 28). • *"It had been anticipated that the observational studies would provide data on the longer term efficacy of omalizumab but, in the event, this was very limited."* (p60) We disagree with the conclusions that the long-term effectiveness data for omalizumab are very limited. Whilst there are clearly more and higher quality data for omalizumab over short-to-medium term durations, this is typically the case where medicines are initially studied in double-blind randomised controlled trials (RCTs), with longer-term studies tending to be open-label extensions of these RCTs or *de novo* open-label observational studies. We are aware of one long-term extension study of an RCT that recruited patients from one of the RCTs that the Assessment Group included as a supportive study:- • **Chung et al. (2005).** This is an extension of the 011	The AG acknowledges the manufacturer's general point that a lack of long-term RCT data is not particular to omalizumab and agrees that long-term observational data are more typically available. We join the manufacturer in awaiting the results of the EXCELS study. We have considered the relevance of the studies the manufacturer specifically identified and evaluated their relevance to the appraisal below. Two were considered to have high relevance and the AG will amend the report to include them. However we note that these two additional studies are small, comprising a total of only 112 patients. The AG searches did not identify the Chung et al. 2005 abstract. However, other abstracts relating to the extension studies related to the 011 trial were identified and were not included in the review for the reason that the 011 trial was excluded (with the exception of the review of steroid sparing): for the reason that the patient population comprised patients who were well-controlled at trial entry. We note that Chung et al. describe their patients as poorly controlled but are unsure as to how this relates to the original trial inclusion criteria. The AG would like to acknowledge that the exclusion of the Britton et al (2011) study constituted an error on their part which partly arose from our inability to obtain additional information beyond that available in the published abstract. This study is highly relevant to the appraisal and, although

		study identified in the Assessment Report as a supportive RCT. Patients were treated in two separate extensions to the core study and received omalizumab for a total of 180 weeks (approximately three and a half years of omalizumab treatment). The authors conclude that: "*Treatment with omalizumab during a 52-week extension study resulted in sustained control of severe persistent allergic asthma similar to that seen in a previous 96-week extension to the 32-week core study.*" This extension study should have been picked up within the n=73 papers identified in the Assessment Group systematic review. However, as a full list of the n=73 studies does not appear to have been provided in the report, we cannot corroborate this. If it was one of the n=73 papers, we are surprised that it receives no mention in the report. There are also some long-term observational data that the Assessment Report could have acknowledged, all of which appear to be relevant to the question of long-term efficacy:- • **Britton et al. (2011)** report long-term observational follow-up of patients (n=52) treated in UK clinical practice. It is not clear from the report why this study has been excluded by the Assessment Group as being *"not relevant study design"* (p259) given that it is a retrospective "before and after" design similar to other studies (e.g. APEX) that are included. This study reports the long-term efficacy of omalizumab in a cohort of UK patients (n=52) with an average exposure to omalizumab of nearly 3 years (982 days), range 16 weeks to over 10 years	small (N = 52), the population reflects that seen in UK clinical practice. Although the baseline exacerbation rate was not reported the levels of unscheduled healthcare use were high. Likewise, other licence criteria such as baseline FEV_1 were not reported. Nevertheless, the AG accepts that since these patients with high hospitalisation rates were treated in UK centres they are likely to meet the NICE guidance/licence criteria. Although data were not reported for all patients and for all outcomes, those that were reported indicate evidence of efficacy across a range of outcomes over substantial periods of follow-up (mean = 982 days). However, the numerical data were not supported by statistical test results. The study provides data on hospital admissions, ER and GP visits, ACT and AQLQ scores and OCS use. We plan to amend the report to include this study. The AG is grateful to the manufacturer for bringing the Storms et al. (2012) paper to our attention as it was published very recently and after the cut-off for our searches. However we consider the relevance of this study to the appraisal to be unclear. Patients were reported as being uncontrolled on ICS with or without LABA and the proportion of patients who were actually receiving LABA was not reported. Additionally the baseline exacerbation rate was reported for only 69/126 patients; of this subgroup only 37 had ≥2 exacerbations in the previous year. Since there were very high attrition rates/incomplete data (only 68 patients by 1 year, 52 at 3 years and 13 at 6 years) it is impossible to determine whether any of the long term data actually relate to relevant patients. The AG is grateful to the manufacturers for bringing to their attention the study of Tzortzaki et al (2012). Published very recently (and beyond the search dates for the review) this appears highly relevant to the appraisal. The 60 patients were treated for four years and key outcomes including what the AG defines as clinically significant exacerbations were reported. The patients appear to closely approximate the

		(3,839 days). The authors concluded that *"...omalizumab substantially reduced the number of hospital admissions/hospital bed days, A&E visits and GP visits, and reduced the requirement for OCS, while improving patient-reported asthma control and QoL"*. • **Storms et al. (2012)** report results from a 6-year observational, retrospective study (n=167) in the US and found that *"...adding omalizumab to the treatment of patients with uncontrolled moderate-to-severe allergic asthma significantly reduced exacerbation rates and associated urgent care visits and hospitalizations and also improved measures of asthma control."* This study appears to have been published after the cut-off date of October 2011 for the Assessment Group systematic review literature searches, although it is uncertain if it could have been picked up by employing a later cut-off date. • **Tzortzaki et al. (2012)** report 4 year observational follow up of patients (n=60) treated in clinical practice in Greece and Cyprus. This study also appears to have been published after the cut off date of October 2011 for the Assessment Group systematic review literature searches. The authors conclude that: "*This long-term "real-life" study demonstrated significant improvement in lung function and other clinical outcomes after omalizumab treatment, evident at 4 months, and sustained after 1 and 4 years suggesting its efficacy in severe allergic asthma, in the "real-life" practice.*"	licence criteria as they were: 1) uncontrolled on step 4 therapy (high dose ICS + LABA) and a minority (27%) were on OCS 2) had a baseline exacerbation rate ≥2/year 3) had FEV_1 < 80% expected OR night-time symptoms (participants had a mean baseline of FEV_1 = 60%) The study showed evidence of efficacy of omalizumab in statistically significant improvementsin exacerbation rate, ACT score and FEV_1 which were sustained over 4 years. Tolerability was also high with no withdrawals due to adverse effects. However the AG notes that this is small (N = 60) non-UK population . We plan to amend the report to include this study.
6	b) Inclusion of Chanez et al	We note the inclusion of Chanez et al. (2010) as one	The AG did not employ a minimum follow-up criterion

	(2010)	of the "licensed population" studies. This was excluded from our systematic review as we included only studies that had a follow up of >16 weeks. The rationale for this was that a minimum of 16 weeks is required, as per the SmPC, to determine response to treatment. Consequently, we felt that only longer-term studies would fully reflect the benefits of treatment with omalizumab. We note that although Chanez et al. (2010) describes a small study population (n=31), the results, where comparisons are possible, are consistent with those seen in larger RCTs. The merits of inclusion of this study are debatable but, as it impacts little in the context of the other much larger included studies, we have no specific concerns. As we highlight in Appendix A, this study seems to have been incorrectly cited as Chanez et al. (2004) throughout the main body of the Assessment Report.	for inclusion in our systematic review, and therefore Chanez et al. met our inclusion criteria (with a duration of 16 weeks). As the manufacturer notes there were few differences between this and the larger RCTs and its impact on the review conclusions was minimal.
Main Comments on the Assessment Report : Clinical Effectiveness: Safety			
7	a. Factual Inaccuracies – Malignancy	The Assessment Report states that "*Statistically higher rates of malignancy were reported in the Summary of Product Characteristics[17], EMEA EPAR[63] and by Corren et al. (2009)[67] ((RR 2.85, 95% CI 1.09 to 7.42). The EMA EPAR suggests against a causal link between omalizumab and malignancy, but further investigations are needed. Four additional publications assessed malignancy rates, none of which reported significant differences between treatment arms.*" (p104). This first sentence of this statement is factually inaccurate and should be amended as none of the three sources cited in the Assessment Report support a "*statistically higher rate*". • We cannot see a relative risk (RR) of 2.85 (95% CI 1.09 to 7.42 cited anywhere in the review by Corren et al.	The statement "statistically higher rates" will be amended in the Assessment Group report to "numerically higher rates". The report will be amended to clarify that the relative risk was calculated by the Assessment Group.

		2009 (reference no. 67 in the Assessment Report). Neither can we see any assertion that there is a statistically higher rate. Corren et al. (2009) acknowledge the numerical difference highlighted in the SmPC and EPAR and further clarify that the incidence of neoplasms in the omalizumab groups was "*consistent with those in the general population, however, the numerical difference, was driven by a lower than expected number of neoplasms in the control arm"*.	
8	b. Interpretation of the evidence that we disagree with – malignancy and arterial thrombotic events	The Assessment Report correctly acknowledges on p103 that: *"The Summary of Product Characteristics[17] highlights... a numerical imbalance in malignancies arising in patients taking omalizumab"*. However, there are three separate statements in the report that should be reviewed by the Assessment Group:- • "*... in particular there is **considerable uncertainty** as to the relationship between omalizumab and the incidences of arterial thrombotic events and malignancies"* (Executive Summary, p28) • "*The evidence on the relationship between omalizumab and the incidence of malignancy is also subject to **great uncertainty***...." (Section 5.6.5, p127) • *"The medium-term adverse event profile of omalizumab indicates **considerable uncertainty** as to the relationship between omalizumab therapy and the incidences arterial thrombotic events and malignancies"* (Section 9.3, p236)	Agree that we will amend the report: • "*... in particular there is **some uncertainty** as to the relationship between omalizumab and the incidences of arterial thrombotic events and malignancies"* (Executive Summary, p28) • "*The evidence on the relationship between omalizumab and the incidence of malignancy is also subject to **some uncertainty***...." (Section 5.6.5, p127) • *"The medium-term adverse event profile of omalizumab indicates **some uncertainty** as to the relationship between omalizumab therapy and the incidences arterial thrombotic events and malignancies"* (Section 9.3, p236)
8	c. Appropriate interpretation of the evidence - malignancy	We note that the Assessment Group systematic review searches were last updated in October 2011, 7 months prior to release of the Assessment Report. Since this time, we are aware of a further pooled analysis (Busse et al. 2012), published in April 2012, that provides updated information. It is uncertain if this analysis could have been picked up by employing a later search cut-off date.	The Assessment Group report was submitted in April 2012 and we therefore did not pick up on this publication. Agree that the Busse (2012) pooled data provides information relevant to the Assessment Group report. Busse (2012) includes malignancy data reported by Buhl (2011) and Starke et al. (2009), as discussed in the Assessment Group report,

		In summary, we do not believe that the available data supports statements of *"considerable uncertainty"* or *"great uncertainty"* regarding the risk of malignancy. We suggest that these statements are revised accordingly prior to the Appraisal Committee meeting.	but also includes additional controlled trial data and analyses. The Assessment Group report will be amended to include the additional statement: A review published after the Assessment Group report submission date (Busse 2012) was considered to include relevant additional evidence on malignancies to support the suggestion that a causal link between omalizumab and malignancy is unlikely. The data reported in Busse (2012) showed numerically higher rates of malignancy with omalizumab in certain study groups, but the differences were not statistically significant (see Table 44). Relevant amendments will also be made to Table 43 (pg 105 of the Assessment Group report) and Table 44 (pg 110 of the Assessment Group report).
9	d. Appropriate interpretation of the evidence – arterial thrombotic events (ATEs)	Information about ATEs was included in the omalizumab Summary of Product Characteristics after an analysis of the clinical trial database in 2010 found a numerical imbalance in omalizumab-treated patients. The difference was not statistically significant and there is no evidence of a causal relationship between omalizumab therapy and ATEs. Further analysis of data from double-blind, placebo-controlled RCTs, including independent external expert adjudication, is ongoing. We agree with the view expressed in the TAR that arterial thrombotic events (ATEs) "*are rare and have not been conclusively linked to omalizumab*" (p127). However, this is at odds with two statements in summary sections elsewhere in the report:- • "*... in particular there is **considerable uncertainty** as to the relationship between omalizumab and the incidences of arterial thrombotic events and malignancies"* (Executive Summary, p28) • *"The medium-term adverse event profile of omalizumab indicates **considerable uncertainty** as to the relationship between omalizumab therapy and the incidences arterial thrombotic events and malignancies"* (Section 9.3, p236)	As per above (b) agree to amend the Assessment Group report: • "*... in particular there is **some uncertainty** as to the relationship between omalizumab and the incidences of arterial thrombotic events and malignancies"* (Executive Summary, p28) • *"The medium-term adverse event profile of omalizumab indicates **some uncertainty** as to the relationship between omalizumab therapy and the incidences arterial thrombotic events and malignancies"* (Section 9.3, p236)

		In summary, we do not believe that the available data supports the statement of *"considerable uncertainty"* regarding the risk of ATEs. We suggest that this statement is revised accordingly prior to the Appraisal Committee meeting.	
10	e. Long-term safety	The Assessment Report concludes the following regarding long-term safety:- • *"It was also not possible to determine long-term safety due to a lack of data over a long-treatment period".* (Executive Summary, p28). • *"...it is not possible to determine its long-term safety due to lack of data over a long-term treatment period."* (p127). • "*Data on serious adverse events of special interest (anaphylaxis, malignancy and thrombotic events) were rarely reported*" (Executive Summary, p28). The Assessment Report should draw a clear distinction between a lack of published data and published data which, due to the rarity of some of adverse events of interest, is likely to be inherently limited. Again, as these statements only appear in summary sections, they are likely to be read out of context by many readers of this report. Extensive malignancy data are summarised in the Assessment Report and section 2c of this response so it is unclear how this could fall into the *"lack of data"* or *"data were rarely reported"* categories.	Agree to change: • *"Long-term safety data were generally limited due either to a lack of published data on the safety of long-term treatment, or the infrequent reporting on some of the adverse events of interest".* (Executive Summary, p28). • *"Long-term safety data were generally limited due either to a lack of published data on the safety of long-term treatment, or the infrequent reporting on some of the adverse events of interest."* (p129). • "*Data on serious adverse events of special interest (anaphylaxis and thrombotic events) were limited*" (Executive Summary, p25).
Main Comments on the Assessment Report: Cost-effectiveness analysis			
11	a. General Modelling approach	We are pleased that the Assessment Group agreed with the overall modelling approach adopted by Novartis and with the majority of the input parameters/assumptions that underpinned our economic evaluation. The large number of scenario analyses across the various patient populations and subgroups appear to have explored the major areas of uncertainty in the economic evaluation. However, they also provide a very large number of different ICERs for the appraisal committee to digest. Our observations on some of the key subgroup/scenario	No response necessary.

		analyses and key elements of the cost-effectiveness analysis are covered in subsequent sections of this response.	
11	b. Subgroups/Positioning	As per our comments during development of TA 133 and TA 201, we agree that clinicians in UK practice tend to position omalizumab in more severe subpopulations of the overall licensed indication population. It is clear from the Assessment Report that, within the constraints of the small subgroup populations in clinical studies, omalizumab tends to be more clinically effective and, therefore, more cost-effective in more severe subgroups. All three of the subgroups described in the Assessment Report represent clinically plausible subgroups for omalizumab i.e. (i) patients hospitalised for asthma in the previous year (the basis for TA 133) (ii) patients receiving maintenance OCS and (iii) patients experiencing $\geq$3 exacerbations in the previous year. We acknowledge the Assessment Group comments in section 5.6.1 (p123) regarding the problematic nature of criteria for multiple exacerbations in clinical practice and the perverse incentives that such criteria might offer both clinicians and patients. Whilst the criteria of the omalizumab licensed indication require patients to have "multiple" documented asthma exacerbations, these issues can potentially be compounded by increasing the requirements for prior exacerbations as seen in TA 133. Nonetheless, the Appraisal Committee for TA 133 agreed in 2007 that the "hospitalisation" subgroup identified a clinically relevant high-risk subgroup. A focus on the maintenance OCS subgroup (with the licence requirement for multiple i.e. $\geq$2 documented exacerbations) could also be considered appropriate. This subgroup is more akin to the SMC recommendation for omalizumab which the Assessment Group acknowledge in section 5.6.1 (p123). It is also the subgroup of patients that clinicians tell us they are increasingly concerned with in UK clinical practice as, aside from the overarching aim of improving asthma control, one of the main goals of treatment with omalizumab is to reduce the requirement for treatment with OCS. This is one of the reasons	No response necessary.

		that Novartis UK collaborated with key severe asthma centres in the UK to develop the APEX study of omalizumab that the Assessment Group include in their review of observational data. On the unanimous advice of severe asthma specialists, the primary endpoint in the APEX study was the reduction in dose of OCS. The Assessment Group acknowledges the methodological limitations of this retrospective before-and-after study, as we did in our submission. Nonetheless, APEX provides some of the richest data on OCS sparing effects of omalizumab that is directly relevant to UK clinical practice. A follow-up study (APEX II) is now underway to provide further data, this time in a prospective setting which should address some of the methodological limitations. We note that the Assessment Group model shows, as our model did, that ICERs for "high-risk" subgroups tend to be lower than ICERs for full study populations. NICE acknowledged that severity of the underlying illness in such subgroups, as well as stakeholder persuasion and significant innovation, were 'special circumstances' that enabled them to recommend omalizumab in TA 133 despite plausible ICERs that were, in NICE's opinion, slightly greater than £30,000 per QALY (Rawlins et al. 2010).	
12	c. OCS Adverse Events (Scenario Analysis No.9)	Continuous use of OCS is well documented to be associated with a wide range of damaging adverse effects. We are therefore greatly encouraged by the willingness of the Assessment Group to attempt to account for the OCS-sparing benefits of omalizumab in their model by adopting a similar approach to the one included in the Novartis model. We suggest that the Appraisal Committee takes full account of the Assessment Group's analysis of the OCS-sparing effects of omalizumab which seeks to quantify the costs saved and utility gained (Scenario Nos. 9A-C). A degree of pragmatism is required to incorporate this type of analysis due to the nature of the data available on OCS adverse effects. However, failure to account for the costs and consequences of OCS-related adverse events in the model is likely to significantly underestimate the cost-effectiveness of omalizumab in UK clinical practice.	The manufacturer states that the 'Assessment Report currently does not appear to provide an indication as to exactly where the data were obtained' for the 'no frills' DALYs. We acknowledge this statement. The 'no frills' DALYs refer to the developed world estimates since no estimates are available for the UK alone. The URL weblink for these estimates is: http://www.google.co.uk/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0CEsQFjAA&url=http%3A%2F%2Fwww.who.int%2Fentity%2Fhealthinfo%2Fglobal_burden_disease%2FDALYMDG_00_2004.xls&ei=zVnkT5nCIuag0QWLp8n0CA&usg=AFQjCNH2XdlwuILXVa2qemtubll-J_qovw

		Whilst the impact of OCS-sparing can be applied to any patient population or subgroup, it clearly has the most relevance and greatest impact in the subgroup receiving maintenance OCS (see section 3b of this response). The APEX study showed that approximately two-thirds of patients receiving omalizumab in UK clinical practice were on maintenance OCS (Niven & Radwan, 2011). Therefore, the scenario of the maintenance OCS subgroup plus the benefit of omalizumab in reducing OCS adverse effects could be considered a possible alternative to the "hospitalisaton" subgroup of TA 133. We note that the Assessment Group acknowledges the OCS-sparing effect of omalizumab in their report: *"Although there are clearly problems with relying on observational data, the evidence of [OCS-sparing] benefit was consistent both across observational studies and with the single open-label RCT subgroup from the licensed population."* Regarding scenario nos. 9A-C, we agree with the Assessment Group that non-age weighted, non-discounted DALYs would ideally have been used to inform the Novartis cost-effectiveness model. However, the only DALY estimates we could locate on the WHO website were for "standard" DALYs (i.e. 3% discounting, age weighting). Figures for what the WHO calls "no frills" DALYs (i.e. no discounting, no age weights) appeared only to be available by country groups or regions rather than at a country-specific level. If the Assessment Group has located UK-specific estimates for "no frills" DALY on the WHO website, they should provide a full web link to the data and/or a full citation. The Assessment Report currently does not appear to provide an indication as to exactly where the data were obtained. If UK-specific "no frills" DALYs are available then we agree with the Assessment Group that the QALY increments outlined in scenarios 9B&C are, in principle, more appropriate for use in a NICE-reference case cost-effectiveness analysis than those outlined in scenario 9A. The caveat to this	The report will be corrected to include reference to the source of the 'no frills' DALYs. The Assessment Group has provided NICE with the data requested by the manufacturer.

		is that without the underlying DALY data and without the OCS adverse effects data in the Assessment Group model (see comments in Section 3j), it is not possible for us to comment on the accuracy of the calculated QALY increments or the cost-effectiveness impact for these scenarios. We agree with the Assessment Group view that further OCS-sparing data for omalizumab would be valuable. As previously stated, the APEX II study will, in time, provide further OCS-sparing data in a prospective UK observational setting. However, it may be increasingly difficult from an ethical standpoint for clinicians to conduct an OCS-sparing RCT (in which patients are randomised to OCS alone) given the consistent signal of effectiveness for omalizumab on this outcome to date that the Assessment Group has highlighted.	
13	d. Asthma-related mortality	The risk of asthma-related death is a key driver of the cost-effectiveness of omalizumab. In this respect, we note the divergence between the Novartis and Assessment Group models in terms of assumptions on this input parameter. The Assessment Group preferred rates from the GPRD study by de Vries et al. (2010) which result in higher cost-effectiveness estimates vs. the Novartis model in which we preferred rates from Watson et al. (2007). We acknowledge that the Assessment Group employs a scenario analysis using the Watson et al. (2007) data in their economic model. We also acknowledge the limitations of the Watson et al. (2007) data that we implemented in our economic model, all of which we described in our submission. Nonetheless, these were the only data located following systematic review that provided a mortality rate for patients experiencing a severe exacerbation (defined in this instance as a hospitalisation for asthma). However, it should be noted that the Watson et al. (2007) data specifically relate to the "hospitalisation" subgroup that forms the basis of TA 133. Whilst the Assessment Group acknowledge, as we did in our submission, that not all	As discussed extensively in the Assessment Report, the asthma-related mortality rate in this patient population is uncertain. In the manufacturer's submission, the Watson et al (2007) data is used for all populations, including the base-case population, and does not specifically relate to the 'hospitalisation' subgroup, which is based on patients who were hospitalised for asthma in the previous year. The mortality rates reported in Watson et al (2007) include all asthma patients, not just those with severe persistent allergic asthma, who were hospitalised for a severe exacerbation.

		exacerbations in omalizumab studies resulted in hospitalisations, the Appraisal Committee for TA 133 recommended omalizumab for use in patients with ≥2 exacerbations resulting in hospital admission or 1 hospitalisation plus ≥2 A&E admissions. In this sense, the Appraisal Committee went beyond the clinical trial evidence to identify a subgroup to which the Watson et al. (2007) data very closely corresponds. Therefore, in the population specifically recommended in TA 133, it is arguable that there should be no downward adjustment of the Watson et al. (2007) data to account for the proportion of exacerbations not resulting in hospitalisation as the Assessment Group suggests. This is because rates of hospitalisation defined in the TA 133 population are at least equivalent to the rates of CSS exacerbations observed in omalizumab clinical studies. The Assessment Group appears to have selected an asthma-related mortality rate from de Vries et al. (2010) that appropriately identifies a high-risk patient population. In this respect they use a rate of 0.4 (57 deaths/2,299 patients) per 100 patient years for patients receiving regular OCS at BTS/SIGN step 5 (defined as more than one OCS prescription in the 3 months before). This clearly aligns more closely to the OCS subgroup analysis in the economic model than other populations or subgroups. However, one of the areas of uncertainty regarding application of this rate to the economic model is the extent to which it could be considered generalisable to the population of patients who would be eligible for omalizumab in clinical practice. In particular, omalizumab patients are required to be (i) uncontrolled (ii) allergic (iii) experiencing multiple exacerbations and (iv) managed by a specialist respiratory physician (in secondary care). It seems that the de Vries et al. (2010) rate is likely to underestimate the risk of death in the population who have the most severe underlying asthma and the highest risk of the key symptomatic event (exacerbations) that is ultimately the cause of all asthma fatalities.	

		In this respect, despite being available for over 6 years in the UK, by the end of 2011 omalizumab was estimated to be used in 1,256 asthma patients in England and Wales (out of 3,744,174), just 0.03% of asthma patients. In contrast, the mortality estimates from de Vries et al. (2010) are derived from a much broader group of step 5 patients, 17,671 out of 507,966 patients (3.48% of the asthma patients in the GPRD database). We acknowledge that understanding the most appropriate rate to employ in model is difficult and it is likely that a degree of pragmatism and interpretation will be required from the Appraisal Committee in this respect. Indeed the Assessment Group acknowledge: "*Although the mortality risk was subject to two independent systematic reviews by the manufacturer and the assessment group, the most appropriate value remains unclear.*" (p29). We note that in TA 133, the Appraisal Committee acknowledged that higher asthma-related mortality rates were likely to be plausible when considering higher risk patient subgroups, for example: • "*It [the Appraisal Committee] was of the opinion that patients who needed more frequent emergency medical attention and hospital admissions than the high-risk hospitalisation subgroup would plausibly have a higher risk of asthma mortality. The Committee concluded that the use of omalizumab was likely to be cost effective in such a subset of patients within the high-risk hospitalisation subgroup*." (TA 133, section 4.7) It is unfortunately not clear from TA 133 what rate the Appraisal Committee thought might be plausible, but if the population was narrow enough, an ICER close to £30K would have required an asthma-related mortality rate of approximately 2% per severe exacerbation. Therefore, we suggest that the Appraisal Committee again gives consideration to application of higher asthma-related mortality rates in higher risk subgroups.	

15	e. Expanded Dose	We agree with the Assessment Group approach of calculating base case cost-effectiveness using *"standard dose"* omalizumab and using separate scenario analysis to assess the potential impact of adding *"expanded dose"* omalizumab. As per our January 2012 submission, we suggest that NICE considers "*standard dose*" omalizumab patients to be a subgroup of those eligible for omalizumab since dosing table expansion in January 2010. In this respect, we note that all of the RCTs included by the Assessment Group tested *"standard dose"* omalizumab only. Furthermore, the TA 133 recommendation is based on patients receiving *"standard dose"* omalizumab. Scenario analysis number 8 (using dosing table expansion) presents costs for a BTS *"expanded dose"* scenario (section 7.4.2.6 and table 94 (p216-217)) which appear to have been calculated using data from Heaney et al. that we supplied as academic-in-confidence in our submission (section 2.2.8.1 & Appendix A). As the calculations for this scenario are based on information that Novartis has provided, we requested an un-redacted version of section 7.4.2.6 from NICE on 6th June 2012. At the time of writing, no response has been received from NICE. Therefore, we cannot comment on the Assessment Group interpretation of the data we supplied or the accuracy of the subsequent calculations in the Assessment Report. What is clear though is that the Assessment Group appears to have implemented only the *"overall"* population costs from the BTS Difficult Asthma registry. The Heaney et al. data also provide an alternative estimate of the increase in patient pool specific to the *"hospitalisation"* subgroup which should have been tested in the scenario analysis. Instead, the costs for the *"overall"* population have been applied to the *"hospitalisation"* subgroup. We also note that the Assessment Group, in estimating the impact of dose table expansion, have used the total costs for the BTS Registry Population i.e. they are comparing *"standard*	The Assessment Group has provided the data requested to NICE. We will add additional clarity to the report to state that the expanded dose refers to both *"standard dose"* plus *"expanded dose.*

		dose" from INNOVATE to *"standard dose"* plus *"expanded dose*" from the BTS Registry. This is not a like-for-like comparison. What the scenario analysis should also include for completeness is application of the *relative* increase in costs observed in the BTS Registry data (for *"expanded dose"* plus *"standard dose"* vs. *"standard dose"* alone) to the INNOVATE *"standard dose"* costs employed in the base case analysis and "hospitalisation" subgroup analysis. Finally, for clarity, it would be helpful if the Assessment Report could make it clear that it is the incremental impact of *"expanded dose"* on overall costs that is accounted for i.e. the ICERs presented are for *"standard dose"* plus *"expanded dose"* patients not *"expanded dose"* patients alone as the Assessment Report currently indicates.	
15	f. Risk of Exacerbations	Asthma exacerbations are the key symptomatic event in patients with severe persistent allergic asthma. Evidence from the APEX study suggests that the frequency of these exacerbations is over twice as high in UK clinical practice as it is in multi-national randomised controlled trials. The Assessment Group scenario analysis no. 2, which assesses the impact of using the baseline exacerbation risk from APEX in the cost-effectiveness analysis, may therefore be more reflective of UK clinical practice.	No response necessary.
16	f. Discount Rate Sensitivity Analysis	We are surprised to see that the Assessment Group does not conduct any sensitivity analysis on the discount rates for costs or health effects in their economic model, particularly as our January 2012 submission illustrated that cost-effectiveness results were particularly sensitive to changes in the discount rate. The Assessment Group acknowledge the observation of this sensitivity on p164 of its report but make no further comment. For example, application of lower discount rates for health effects substantially improves the ICER in the Assessment Group model e.g. reducing the discount rate to 1.5% for outcomes as per NICE's recent methods guide update for	The Assessment Group considered that the application of differential discount rates was not appropriate in this situation, where the benefits from treatment are not sustained after treatment discontinuation. However, the Assessment Group can present such analysis if the Committee finds it appropriate.

		discounting in special circumstances decreases the ICER by approximately 20%. On this point, NICE states that "*Where the Appraisal Committee has considered it appropriate to undertake sensitivity analysis on the effects of discounting because treatment effects are both substantial in restoring health and sustained over a very long period (normally at least 30 years), the Committee should apply a rate of 1.5% for health effects and 3.5% for costs.*" This is important as omalizumab appears to fit these criteria in terms of offering substantial and sustained health benefit. For example, in the Assessment Group model, treatment with omalizumab is associated with large utility gains over the full treatment duration in most scenarios and with reduced asthma-related mortality which is extrapolated over a lifetime time horizon.	
16	g. Cost-effectiveness of omalizumab in children aged 6-11 years	We are pleased to see that the Assessment Group have adopted a pragmatic approach to interpretation of the limited evidence in children, for example: *"Given that the randomised data in children who meet the licence criteria is so restricted, limited as it is to this single subgroup, it may be reasonable to extrapolate supportive evidence from the data in adults and older children. This is particularly the case in considering children who are dependent on maintenance OCS, of whom only 6 were included in IA-05-EU-P."* (p122). This type of approach is essentially what underpins the approach of many HTA bodies who implement more pragmatic "abbreviated" assessments when a medicine has already been approved for the main indication in an adult population. The Assessment Group's pragmatism on this point is reflected in the cost-effectiveness analysis with the assumption that children aged 6-11 years gain the utility benefit observed for patients aged 12 years and older. However, the Assessment Group does not appear to go further than this, as it implied might be reasonable when considering an OCS subgroup in the 6-11 years age group. We note that the Assessment Report contains some Academic-in-Confidence Data from a recent unpublished trial by Brodlie et	No response necessary.

		al. (2011) (reference 39 in the Assessment Report). The unpublished nature of these data means that they were not picked up by our systematic review but we understand that a publication has been accepted by the authors for publication by the Archives of Disease in Childhood. We suggest that the Assessment Group considers a pragmatic OCS-sparing analysis in children using data from Brodlie et al. (2011) and extrapolation of exacerbation/utility data from OCS subgroups of trials in adults and adolescents. Such an analysis could additionally include the potential growth impairment impact of OCS using the assumptions from NICE TA 188 that we highlighted in Appendix G of our submission.	
17	h. Base-case utilities – EXALT vs INNOVATE	We note that the Assessment Group have utilised EXALT utilities rather than INNOVATE utilities in their base case analyses. There is clearly a difficult trade-off between using mapped utilities from a double-blind RCT (INNOVATE) and direct EQ-5D utilities from an open-label RCT (EXALT). The only notable difference in utility across all populations is seen in the overall population where the utility difference between omalizumab and placebo is significantly smaller in the EXALT study (whereas for all of the subgroups, there is close agreement on the utility difference). It may be academic as the TA 133 recommendation focuses on subgroup populations but the Assessment Group has chosen the lower of the two differences (0.048) in the base case and the higher of the two (0.110) in scenario analysis no. 5. This presents a "worst case" base case analysis which may not be reasonable in light of the available utility evidence.	No response necessary.
17	i. Errors and Omissions of Data in the Assessment Group Model	We believe that there is an error in the way that the Assessment Group has implemented the asthma-related mortality rates in the 'Asthma Death' worksheet of the economic model. The Assessment Group appears to have converted the mortality rate from de Vries et al. (2010) to a probability. The resulting probability of asthma death is then	The Assessment Group has provided the data requested to NICE. Response to errors in the model is in the last section of the table (p13-14).

		adjusted in the model by the relative risk (RR) of a CSS exacerbation. For scenario analysis no. 4 employing data from Watson et al. (2007), the rate of mortality has not first been converted to a probability, even though the column title (cell J14) indicates that cells J16:J436 contain probabilities. This rate is then multiplied by the probability of a CSS exacerbation (i.e. the Assessment Group have converted the rate of a CSS exacerbation to a probability). Despite the inconsistency regarding the initial handling of the mortality rates from the literature, in both scenarios a probability of mortality is being multiplied by a RR of a CSS exacerbation in the model. The literature indicates that it is methodologically incorrect to multiply a probability by a RR:- • *"It is common to include treatment effects as multiplicative, perhaps as relative risks, or in terms of treatment effects estimated directly from a survival analysis, in terms of hazard ratio. Such a treatment effect should not be applied directly to the baseline transition probability; rather, the treatment effect (call this τ) should instead be applied to the hazard rate... it would be incorrect to multiply the treatment effect by the baseline probability."* Briggs, Claxton & Sculpher (2006), p53. • *"The adjustment of the rate with the relative risk cannot be performed directly with probabilities."* Fleurence & Hollenbeak (2007). We have proposed full amendments to the Assessment Group model in the separate proforma as requested by NICE. The difference between implementing rates vs. probabilities in the asthma-related mortality calculation has little impact in the model when using lower mortality rates like the 0.004 annual rate per patient in de Vries et al. (2010). However, if employing higher rates in the model, the Assessment Group approach appears to consistently underestimate the cost-effectiveness of omalizumab. Therefore, we do not believe that the Assessment Group model provides a sound basis for estimating the impact of increasing the mortality rate as outlined in scenario number 4. We also note that the Excel file does not include model input data for some of the scenario analyses or basic direction on how to run them. For some of these scenarios, we can deduce what the Assessment	

		Group appear to have done from the information in the Assessment Report. However, this is not the case for scenarios 9A-C (Adverse Effects of OCS) where it is unclear to us how the cost and utility data are being implemented in the model. One would assume that the costs and utilities are fully incorporated into the model analysis to allow them to be discounted appropriately as per the other costs and benefits. The Assessment Report (p218) supports that this is the case by stating that *"a 3.5% annual discount rate is applied to the DALYs in the model"*. However, we cannot find any OCS adverse effects data in the Excel file that would allow implementation in this way. We requested clarification from NICE on 6th June 2012 regarding how the Assessment Group have incorporated this OCS adverse events analysis but, at the time of writing, have yet to receive a response. Consequently, whilst we fully endorse the full exploration of OCS adverse effects in the Assessment Group model, we are unable to verify or replicate any of the cost-effectiveness results presented for scenarios 9A-C.	
18	j. Drop-out rate scenarios	Although we accounted for a drop out rate in the economic model to illustrate the potential impact on cost-effectiveness, there are significant limitations to this approach when using the data from an ITT analysis of an RCT. This is because the patients that drop out still contribute to the treatment effect i.e. they dilute the treatment effect observed in patients remaining in the trial. Therefore, the Assessment Group sensitivity analysis presented in table 99 whereby the withdrawals from omalizumab treatment are set to 10% and 20% should be interpreted with caution due to the potential for double-counting.	No response necessary.
Minor Comments and Factual Inaccuracies			
39	3.3.3, Paragraph 1	This paragraph cites information slightly out of context and overinflates the potential number of future patients on omalizumab. It should acknowledge that a proportion of all patients initiated will be non-responders. For example, in our estimates, we assumed that 82.4% of patients will respond to Xolair in line with data from UK clinical practice (APEX study).	The AG is happy to incorporate an acknowledgement that a proportion of these patients will be non-responders and will not continue to receive omalizumab beyond 16 weeks.
39	3.3.3, paragraph 2, lines 2 & 5	Two mentions of *"...children aged 6 to 12 years..."*. These should say 6 to 11 years.	P39 3.3.3 The AG acknowledges the error and will amend to read "children aged 6 to 11 years"
41	5.1.1.1	As mentioned elsewhere in our response, we are a little	No response required

		surprised that the systematic review searches were last run in October 2012, seven months prior to dissemination of the Assessment Report. A search update closer to the report release date might have located additional information relevant to the review – for example the source of malignancy information by Busse et al. (2012) and some additional long-term efficacy studies.	
51	Table 2	The study by Chanez et al. is referred to throughout the document as Chanez et al. (2004) but is actually Chanez et al. (2010) as per the citation in the Assessment Report reference list.	The AG acknowledges the error and will amend throughout
62	Table 7, % of patients with good/excellent GETE rating in omalizumab arm of IA-05 EUP	Should read 76.7 not 74.0	The AG acknowledges the error and will amend
63	Table 8, Trial IA-04	Should read IA-04 EUP not IA-04	The AG acknowledges the error and will amend
67	Table 12, Pooled Estimate of INNOVATE and EXALT	The incidence rate for omalizumab and comparator is missing from the table. Furthermore, although the Assessment Report states that figures in the table were obtained from the manufacturer submission, we cannot locate any of these data in our submission. We assume that for the mean rates, these were calculated by subtracting the CSS exacerbation rate from the CS exacerbation rate. We also assume that the Assessment Group has derived the confidence intervals for the rate ratios.	The incidence rate for omalizumab should read 0.374 whilst the incidence rate for comparator should read 0.488. These data were derived from the data provided in the economic section of the manufacturer's submission (Appendix C) . In addressing this comment the AG noted that pooled incidence rates for CSS exacerbations were also missing from Table 11: these should read 0.233 for omalizumab and 0.447 for comparator. We will clarify this in the report and make it clear where numbers were calculated by the manufacturer or the AG respectively.
69	Table 14, Rate Ratio, INNOVATE, Total Exacerbations	Should read 0.662 not 0.293	The AG acknowledges the error and will amend
73	5.3.4.7, paragraph	*"... but only EXALT showed a statistically significant benefit*	These data were derived from the data provided in

	3, line 2	*for CSNS exacerbations."* CS exacerbations are made up of CSS and CSNS exacerbations. CSNS exacerbations are CS exacerbations minus CSS exacerbations. The rate of CSNS exacerbations is not a statistical calculation in the clinical studies so we are unclear how the cited data are derived.	the economic section of the manufacturer's submission (Appendix C). We will clarify this in the report and make it clear where numbers were calculated by the manufacturer or the AG respectively.
76	Table 23, EXALT ER Attendance	"0.332 (0.186 (0.057 to 0.613)" should read "0.186 (0.057 to 0.613)"	The AG acknowledges the error and will amend
76	Table 23, IA-05 EUP ER Attendance	"1.417 (0.767-2.62)" should read "1.467 (0.514, 4.191)"	The AG acknowledges the error and will amend
82	Table 28, Chanez et al. "2004", Comparator Difference	Should read 0.3 (-4 to 2) not 1.0 (-22 to 4)	The AG acknowledges the error and will amend
83	5.3.6.4, paragraph 1, line 6	*"The observational studies APEX and eXperRience showed evidence of benefit on symptom scores but did not report statistical test results".* For symptom scores in APEX, we assume that the Assessment Report is referring to the Asthma Control Test (ACT). If so, the differences observed for pre-omalizumab vs. post-omalizumab were statistically significant.	The manufacturer's submission states that, of the observational studies, only PERSIST reported on clinical symptom scores (p60); we note that the publication (Barnes 2011) does not report statistical test results but does report that there were significant differences from baseline: the AG is happy to amend the report to reflect this statement.
89	Table 34, IA-05 EU subgroup, Time point assessed (weeks)	Should read 52 not 24	These data were taken from the manufacturer's submission tables 3.11 and table 3.12 and do relate to the 24 week time point, which is the correct timepoint for the primary outcome before the steroid sparing phase of the trial. The AG does however acknowledge that 52 week data were reported and is happy to incorporate these data into the report.
90	5.3.9.2, paragraph 1, penultimate line	56.7 should read 56.7%	The AG acknowledges the error and will amend
94	Studies not included in evaluation	*"Although Barnes 2012 reported a follow up of 12 months, only outcome data at 16 weeks were reported."* This is not	The publication (Barnes 2012) did not report these data; the AG acknowledge that these data were

	of long-term response	correct, data were reported for up to 12 months follow up, but clearly different patients will have been followed up for different durations within this timeframe.	available in the manufacturer's submission and will amend accordingly
103	5.52, paragraph 1, line 3	*"The manufacturer's submission did, however, report a statistically significant reduction in serious adverse events in patients treated with omalizumab (RR 0.49, 95% CI 0.26 to 0.94)."* This statement has been taken a little out of context. As described in table 43, this statement describes the finding in one of the 4 double-blind RCTs (IA-05) for which we provided detailed adverse event listings in our submission. The statement could be made more accurate by adding *".... in one of the four double-blind RCTs that were described."*	Agree to amend the Assessment Group report: "*The manufacturer's submission did, however, report a statistically significant reduction in serious adverse events in patients treated with omalizumab (RR 0.49, 95% CI 0.26 to 0.94) in one of the four double-blind RCTs that were described."*
107	Table 43, Novartis Manufacturer's Submission MTA, General Findings on Adverse Effects	"*bronchitis, ear infection, gastroenteritis".* These three words appear with no context.	Acknowledge and accept this is a mistake and agree to delete from Table 43.
121	Table 47, Comments Column	*".... under estimated? Include in model?".* For sleep disturbance, mood problems and weight gain, these words appear with no context.	Acknowledge and accept this is a mistake and agree to delete from Table 47.
155	6.3.5.1, paragraph 2, line 6-7	"*The manufacturer did not present the impact of the dosing expansion on the average cost of omalizumab per patient and the ICER estimates*". This is not correct. We outlined the impact of the dose table expansion in the overall population and in the NICE TA 133 population (see section 2.2.8.1 and Appendix A of our submission). The impact of the cost increase per patient on the ICER was tested in sensitivity analysis (section 4.6.2, table 4.19, and section 4.7.2.1, table 4.23).	We acknowledge that the impact of the dose table expansion was explored in the one-way sensitivity analysis conducted by the manufacturer. We will correct the sentence in the report.
155	6.3.4.1	*"Asthma-related deaths should have been removed from the life tables".* We concede that this should have been done for complete accuracy but also agree with the Assessment Group view that *"this is unlikely to be a significant issue"*	No response necessary.
160	6.3.6.2	*"The manufacturer uses the absolute HRQoL value at end of follow-up for an exacerbation requiring OCS use and asthma-related hospitalisation reported in Lloyd et al (2007)[93] instead of the difference in HRQoL between baseline and follow-up (mean change from baseline in Table 58). This appears particularly important since it is the decrement in HRQoL due to these events that should be incorporated in the model."* We agree with the Assessment Group that applying a utility	No response necessary.

		decrement based on Lloyd et al. (2007) is the more correct approach, although we acknowledge that this makes little difference to the cost-effectiveness.	
171	Para 1, line 4	001 should read 011	We acknowledge the inaccuracy. The trial number will be corrected in the report.
181	Final paragraph	56% should read 57% if 56.5% is being rounded	We acknowledge the inaccuracy. The percentage will be corrected in the report.
186	Table 71, Average cost of omalizumab per annum	As per our email to the NICE Project Manager on 4th May 2012, we are anticipating European Commission approval of a minor change to the omalizumab dosing table in mid-June 2012. The total omalizumab dose per dosing table cell will be unchanged, hence there will be no impact on omalizumab drug costs. However, some patients may benefit from moving to less frequent q4wk administration which would result in fewer administrations per year and slightly reduced administration costs. As administration costs are relatively low in the Assessment Group model, any improvement in cost-effectiveness is likely to be very small.	No response necessary.
201	7.4.2.1, paragraph 2	*"Patients enrolled in INNOVATE had their therapy optimised before the trial commenced, whereas some patients in clinical practice may not be fully optimised before receiving omalizumab."* In UK clinical practice, patients are very carefully selected for omalizumab. It is almost certain that the vast majority of patients will be very carefully optimised on current therapies before omalizumab is added. TA 133 also specifies that this should be the case. Clinical Advisors to the Assessment Group and other UK Clinical Experts should be able to corroborate this.	This sentence should be interpreted in its context: *"The exacerbation rates from APEX are considerably higher than the baseline rates from INNOVATE. The data suggests that patients in UK clinical practice may experience exacerbations more frequently than observed in a clinical trial. Patients enrolled in INNOVATE had their therapy optimised before the trial commenced, whereas some patients in clinical practice may not be fully optimised before receiving omalizumab. "*
Errors in the Assessment Group Model			
Model	'Asthma Death' worksheet	The difference between implementing rates vs. probabilities in the asthma-related mortality calculation has little impact in the model when using lower mortality rates like the 0.004 annual rate per patient in de Vries et al. (2010). However, if employing higher rates in the model, the Assessment Group approach appears to consistently underestimate the cost-effectiveness of omalizumab. Therefore, we do not believe that the Assessment Group model provides a sound basis for estimating the impact of increasing the mortality rate as outlined in scenario number 4. Results obtained from the proposed amendment of the Assessment Group Model are as follows:-	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).

		<table><tr><th>Population</th><th>Assessment Group ICERs (£/QALY)</th><th>Revised Assessment Group ICERs (£/QALY)</th></tr><tr><td colspan="3">Base Case Analyses & Subgroups (using asthma-related mortality from de Vries et al. (2010))</td></tr><tr><td>Overall Population: Adults & Adolescents</td><td>83,822</td><td>83,680</td></tr><tr><td>Overall Population: Paediatric</td><td>78,009</td><td>77,937</td></tr><tr><td>Hospitalisation Population: Adults & Adolescents</td><td>46,431</td><td>46,483</td></tr><tr><td>Hospitalisation Population: Paediatric</td><td>44,142</td><td>44,144</td></tr><tr><td>OCS Population: Adults</td><td>50,181</td><td>50,161</td></tr><tr><td colspan="3"><u>Scenario 4 Analyses</u></td></tr><tr><td>Overall Population: Adults & Adolescents</td><td>46,029</td><td>43,652</td></tr><tr><td>Overall Population: Paediatric</td><td>98,688</td><td>96,211</td></tr><tr><td>Hospitalisation Population: Adults & Adolescents</td><td>31,576</td><td>29,856</td></tr><tr><td>Hospitalisation Population: Paediatric</td><td>47,430</td><td>46,372</td></tr><tr><td>OCS Population: Adults</td><td>29,657</td><td>27,264</td></tr></table>	
Model	Cell F16 and B9	This change only impacts the analyses for scenario no. 4 in which patients are aged <12 years. The impact on these two scenarios is very slight as the table below illustrates. <table><tr><th>Population</th><th>Assessment Group ICERs (£ per QALY gained)</th><th>Revised Assessment Group ICERs (£ per QALY gained)</th></tr><tr><td colspan="3"><u>Scenario 4 Analyses</u></td></tr><tr><td>Overall Population:</td><td>98,688</td><td>98,874</td></tr></table>	We acknowledge the error and accept the correction.

		Paediatric				
		Hospitalisation Population: Paediatric	47,430	47,290		
		.				