Additional Cost-Effectiveness Analyses (Using Assessment Group Model)

This document should only be considered in conjunction with our ACD response dated 30th November 2012. Please note that information highlighted in yellow in this document is considered Commercial-in-Confidence.

1. Background

As described in our separate ACD response, there is a lack of clarity in the omalizumab ACD on what the Appraisal Committee considers to be:-

- The most appropriate Subgroup population
- The most plausible asthma mortality rate
- The most plausible ICER; and
- The most appropriate proportion of children to use in weighted average ICER calculations

To clarify these issues we spoke with Meindert Boysen and Elisabeth George by telephone on Tuesday 6th November and, having sought further clarity from the Appraisal Committee Chair Dr Amanda Adler, we received a follow up call from Elisabeth George on Thursday 8th November. Based on these conversations, our understanding is as follows:-

- Our assessment of Subgroup 1 (maintenance OCS and hospitalisation for asthma in the previous year) not being favoured by the Appraisal Committee is 'reasonable' based on the content of the ACD and Evaluation Report
- Whilst subgroup 2 (maintenance OCS) appears to be more appropriate to UK clinical practice than subgroup 1, our assessment of **Subgroup 3 (maintenance OCS or >=4 courses of OCS in the previous year)** being the preferred subgroup of the Committee is 'reasonable' based on the content of the ACD and Evaluation Report
- The main concern and key remaining area of uncertainty for the Committee is the impact on the 'new' mortality data from de Vries et al. (2010) on the cost-effectiveness of omalizumab
- Based on the content of the ACD and Evaluation Report it would be 'reasonable' for us to test the impact on cost-effectiveness of implementing 'mid-point' mortality rates (i.e. between Watson et al. and de Vries et al) in the Assessment Group model to arrive at a point estimate ICER.
- It would also be 'reasonable' for us to implement the 'mid-point' rate in the Watson et al. calculations of the economic model (with mortality varying by age, which appears to be favoured by the Appraisal Committee based on the content of the ACD) rather than in the de Vries calculations of the economic model (where the rate of mortality does not vary by age)
- As the 'most plausible' ICER range in the ACD of £31K-£42K per QALY is based on mortality rates inflated by +15%, it would be 'reasonable' to assume that the +15% assumption is favoured by the Appraisal Committee to account for severity of illness

- It would be 'reasonable' for us to test alternative proportions of children in the weighted average ICER calculations, under various mortality rate assumptions, to address the Committee's concerns on the proportion of children potentially being an underestimate
- We are permitted to submit 'new' cost-effectiveness analysis to address the above uncertainties in the Assessment Group model. This 'new' analysis is presented in this document, separately to our ACD response, at the request of NICE.

In our ACD response, 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.

Based on the clear feedback from clinical specialists and patient experts, the Appraisal Committee has *"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). These limitations included perverse incentives for patients to seek hospitalisation to quality for treatment and, conversely, patients choosing not to go to hospital even when extremely ill. Given the clear feedback from stakeholders and the view of the Committee, Novartis believes that there is no sound basis for recommending 'previous hospitalisation' as the sole eligibility criteria for omalizumab treatment. We also note the clear feedback from clinical specialists as follows *"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). Therefore, the PAS has been designed specifically for Subgroups 2 or 3 only. As such, the PAS would not apply to Subgroup 1 or the current population as defined in TA133 in which the 'previous hospitalisation' criterion is applied. As described in detail in our ACD response, we strongly believe that **Subgroup 3 i.e. patients on maintenance OCS or >=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.

As this PAS is currently under consideration by PASLU and DH, all of the ICERs presented in this document are shown with and without PAS for completeness.

2. 'New' Analyses Using Assessment Group Model

a. Version of Model Used for Analyses

The model version used for these analyses is the version supplied to Novartis by NICE on 27th September 2012 with the file name ***"Copy of Omalizumab subgroup 1 base-case.xlsm"***.

b. Calculation of a 'Mid-Point' Mortality Rate

We note the following key comments in the ACD:-

- *"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)*
- *"The committee concluded that it was inappropriate to accept the same mortality risk across all ages as it did not reflect the expected natural history of the disease"* (ACD, 4.4.9, p46)
- *"The Committee concluded that, even assuming 15% higher mortality rates because of the severity of the disease, the ICERs were still high at £31,000 and £42,000 per QALY gained using the Watson et al. or De Vries et al. data respectively" (ACD, 4.4.15, p51)*

We have therefore concluded the following based on the above statements:-

- Based on the first point we assume that a mortality rate 'in between' the Watson et al. and de Vries et al. estimates equates to a 'mid-point' rate.
- Based on the second point, we assume that the Appraisal Committee has a preference for cost-effectiveness analysis using the Watson et al. mortality calculations (in which asthma mortality varies by age) rather than mortality calculations based on de Vries et al. (which employ a flat rate that does not vary by age).
- Based on the third point, we note that the 'most plausible' ICER range stated in ACD is based on mortality rates inflated by +15%. We have therefore adopted this assumption in all of our calculations.

In the latest Assessment Group model version, inflating Watson et al. rates by +15% provides the following mortality rates:-

- 6-11 years – 0.112%
- 12-16 years – 0.367%
- 17-44 years – 0.440%
- >=45 years – 2.850%

In the latest Assessment Group model version (i.e. using 2.2% children), the weighted average asthma mortality rate based on the inflated rates above is **1.45%.**

- (2.2% x 0.112%) + (6.5% x 0.367%) + (48.9% 0.440%) + (42.4% x 2.850%) = **1.45%**

- This is the weighted average rate that underpins the Assessment Group ICER of £31K per QALY (which is specific to Subgroup 3)

In the latest Assessment Group model version (i.e. using 2.2% children), the asthma mortality rate is based on de Vries et al. rates +15% i.e. 0.4% x 1.15 = **0.46%.** This is the rate that underpins the Assessment Group ICER of £42K per QALY (which is specific to Subgroup 3).

The 'mid-point' mortality rate between 1.45% and 0.46% is 0.955%. To arrive at this weighted average rate based on Watson et al. calculations (which include the age variation) the following mortality rates need to be implemented in the Assessment Group Model:-

- 6-11 years – 0.073%
- 12-16 years – 0.242%
- 17-44 years – 0.290%
- >=45 years – 1.877%

c. <u>Alternative Proportions of Children used in Age-Weighted ICER Calculations</u>

As stated in our ACD response, 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.

Testing alternative proportions of children in the Assessment Group model has two related impacts:-

1. It deflates the proportion of patients at other ages >=12 years
2. This in turn, reduces the weighted average Watson et al. mortality rate and therefore reduces the mid-point mortality rate (given that the de Vries et al. rate remains fixed for patients of all ages)

The various proportions of patients by age and the mortality rates employed in these scenarios are calculated as per the workings out described in section 2b and are presented in table 1 overleaf, alongside the 2.2% scenario for comparison:-

Table 1 – Asthma Mortality Rate According to Proportion of Children Aged 6-11 Years

Age (years)	Model based on 2.2% of children aged 6-11 years			Model based on 4.75% of children aged 6-11 years			Model based on 7.3% of children aged 6-11 years		
	Proportion of Patients	Mortality Rate (Watson et al.) +15%	Mortality Rate (Mid-Point, Age-Weighted) +15%	Proportion of Patients	Mortality Rate (Watson et al.) +15%	Mortality Rate (Mid-Point, Age-Weighted) +15%	Proportion of Patients	Mortality Rate (Watson et al.) +15%	Mortality Rate (Mid-Point, Age-Weighted) +15%
6-11	2.2%	0.112%	0.073%	4.75%	0.112%	0.074%	7.30%	0.112%	0.074%
12-16	6.5%	0.367%	0.242%	6.33%	0.367%	0.243%	6.16%	0.367%	0.245%
17-44	48.9%	0.440%	0.290%	47.63%	0.440%	0.292%	46.35%	0.440%	0.294%
>=45	42.4%	2.850%	1.877%	41.29%	2.850%	1.888%	40.19%	2.850%	1.900%
Weighted Average Mortality Rate		1.450%	0.955%		1.415%	0.937%		1.380%	0.920%

d. Cost of Omalizumab With and Without PAS

The costs of omalizumab with and without the PAS that is currently under consideration by the DH/PASLU are shown in table 2 below:-

Table 2 – Costs of Omalizumab With and Without PAS

Dosage Form	Cost of omalizumab without PAS (i.e. list price), excl. VAT	Cost of omalizumab with PAS, excl. VAT (PAS is a simple confidential discount of [redacted]
150 mg/1 ml	**£256.15**	[redacted]
75 mg/0.5 ml	**£127.08**	[redacted]

e. Results of 'New' Analyses Using Assessment Group Model

Cost-effectiveness results are presented in table 3 overleaf. Results are presented for Subgroups 2 and 3 only, and not Subgroup 1, for the reasons described in section 1 of this document and section A2 of the ACD response.

Table 3 – ICERs based on Mid-Point Mortality and Varying Proportions of Children – Presented With and Without PAS

Subgroup	Mortality Assumption	Proportion of Patients Aged 6-11 Years					
		2.2%		4.75%		7.3%	
		ICER (Without PAS)	ICER (With PAS)	ICER (Without PAS)	ICER (With PAS)	ICER (Without PAS)	ICER (With PAS)
2 (Maintenance OCS)	Watson et al. +15%	£32,134*	£22,077	£32,879	£22,573	£33,631	£23,097
	'Mid-point' (age weighted) +15%	£35,245	£24,183	£35,936	£24,591	£36,607	£25,010
	De Vries et al. +15%	£42,634*	£28,835	£42,842	£29,048	£43,079	£29,250
3 (Maintenance OCS or >=4 courses of OCS in the previous year	Watson et al. +15%	£31,159*	£21,473	£31,953	£21,979	£32,739	£22,467
	'Mid-point' (age weighted) +15%	£34,254	£23,453	£34,955	£23,902	£35,597	£24,370
	De Vries et al. +15%	£41,688*	£28,311	£42,136	£28,542	£42,471	£28,757

* Figures presented by Assessment Group in 'Additional analyses requested by NICE on behalf of the Committee'. All other figures calculated by Novartis using a modified Assessment Group model.

Cost-effectiveness results **WITHOUT PAS** show that irrespective of the choice of Subgroup (2 or 3) or the proportion of children (2.2%, 4.75% or 7.3%):-

- ICERs based on the 'highest' mortality rate of Watson et al. +15% range from £31K-£34K per QALY
- ICERs based on the plausible 'mid-point'(age weighted) mortality rate +15% range from £34K-£37K per QALY
- ICERs based on 'lowest' mortality rate of de Vries et al. + 15% range from £42K-£43K per QALY.

Cost-effectiveness results **WITH PAS** show that irrespective of the choice of subgroup (2 or 3) or the proportion of children (2.2%, 4.75% or 7.3%):-

- ICERs based on a 'highest' mortality rate of Watson et al. +15% range from £21K-£23K per QALY
- ICERs based on the plausible 'mid-point' (age weighted) mortality rate +15% range from £23K-£25K per QALY
- ICERs based on 'lowest' mortality rate of de Vries et al. + 15% range from £28K-£29K per QALY.

f. Discussion

Adopting 'mid-point' mortality values in the Assessment Group model yields ICERs that are closer to those resulting from adoption of the Watson et al. rates than de Vries et al. rates. In this respect, the relationship between the asthma mortality rate and the ICER is non-linear and ICER decreases flatten out progressively as the asthma mortality rate increases. This is potentially important from a policy decision perspective as it means that ICERs based on mortality rates between Watson et al. and de Vries et al. trend towards the lower end of the £31-£42K per QALY range cited in the ACD for Subgroup 3.

Irrespective of the choice of Subgroup (2 or 3) or the proportion of children (2.2%, 4.75% or 7.3%), all ICERs **WITH PAS** based on the plausible 'mid-point' mortality rate +15% are **≤£25K per QALY** and all ICERs based on 'lowest' mortality rate of de Vries +15% are **≤£29K per QALY**. Implementing the 'highest' mortality rate of Watson et al. +15% results in ICERs **≤£23K per QALY**. Therefore, all ICERs are comfortably under £25K per QALY when adopting the 'highest' mortality rate, approximately £25K per QALY using a plausible 'mid-point' rate and remain under £30K per QALY, even when adopting 'lowest' mortality rates that the committee consider to be underestimates for the 'very severe' patient populations under consideration *(ACD, 4.4.9, p47)*. We hope that the submitted PAS will fully address the concerns of the Appraisal Committee on the key remaining areas of uncertainty in the Assessment Group model.

As stated in section A2 of our ACD response and in section 1 of this document, we believe that Subgroup 3 is the most clinically relevant Subgroup based the ACD content and input received by NICE from clinical experts in the Evaluation Report. Whilst ICERs between Subgroups are similar, the ICERs for Subgroup 3 are consistently lower than those of Subgroup 2 by approximately £500-£1,000 per QALY. Therefore, as well as being the most clinically relevant subgroup, Subgroup 3 is also the population for which omalizumab represents the most cost-effective use of NHS resources.

g. Changes Made to Assessment Group Model

An example model file is provided with this additional analysis document as follows:-

- ***'Omalizumab Model_subgroup 3_4.75% children_mid-point Watson mortality+15% - RUN.xlsm'***

This illustrates the changes made to the Assessment Group Model to arrive at the results based on 'mid-point' mortality rates and alternative proportions of children that are presented in this document:-

- The calculations of 'mid-point' mortality rate and adjusted proportions of children aged 6-11 years are made in the green shaded cells on the '**Results Table**' worksheet. The proportions of children in **cells L14:31** were used to overwrite the content of **cells L6:L9** as appropriate depending on the desired proportion of children aged 6-11 years.

To run the model with the original Watson et al. mortality rates +15% or de Vries et al. mortality rates +15%, the following changes were made:-

- On the '**Asthma Death**' worksheet of the original Assessment Group model file, **cell B5** (de Vries et al.) or **cells L7:L10** (Watson et al.) were multiplied by **1.15.** The relevant mortality data source was selected using **cell C26** on the ***'Parameters'*** worksheet.

To run the model for the **WITH PAS** scenarios, the following change was made:-

- Cell C20 of the '**Parameters**' worksheet was changed to [redacted]

Copies of the model files for each of the 32 'new' ICERs presented in table 3 can be supplied by CD-Rom on request if this would be helpful.